

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761042Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## MEMORANDUM

**To:** File for Amgen, Inc.'s BLA 103795 for Enbrel (etanercept)

**From:** The CDER Exclusivity Board

**Re:** Exclusivity Expiry for Enbrel (etanercept) BLA 103795

**Date:** August 5, 2015

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The CDER Exclusivity Board (Board) has determined that there is no unexpired exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Enbrel (etanercept) (BLA 103795; Amgen, Inc.) that would prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Enbrel (etanercept).

Section 351(k)(7)(A) of the PHS Act states that “approval of ... [a biosimilar application] may not be made effective by the Secretary until the date that is 12 years after the date on which the reference product was first licensed under subsection (a).” Section 351(k)(7)(B) of the PHS Act states that ... [a biosimilar application] may not be submitted to the Secretary until the date that is 4 years after the date on which the reference product was first licensed under subsection (a).” Under section 351(k)(7)(C)(i) – (ii) of the PHS Act, exclusivity is not available for a supplement to the reference product or a subsequent application filed by the same sponsor for a: (1) non-structural modification to the product that results in a new indication, route of administration, dosage schedule, dosage form, delivery system, delivery device, or strength, or; (2) a structural modification that does not change the product’s safety, purity, or potency.

After reviewing the record, the Board concludes that BLA 103795 for Enbrel (etanercept) was first licensed by FDA under section 351(a) of the PHS Act on November 2, 1998. Additional supplements for changes and updates to the approved labeling were approved after this date of first licensure.

The dates that are 4 and 12 years after the date of first licensure of Enbrel (etanercept) are November 2, 2002, and November 2, 2010, respectively. A licensure of a supplement does not trigger a separate period of exclusivity. Accordingly, section 351(k)(7) of the PHS Act does not prohibit the submission, or approval, of any 351(k) application for a proposed biosimilar (or interchangeable) to Enbrel (etanercept).

**Cc:** Marlene Schultz-DePalo, CDER Purple Book Manager, Office of Biotechnology Products, CDER;  
Therapeutics Biologics and Biosimilars Staff, Office of New Drugs, CDER;  
Sandra Benton, Office of Medical Policy, CDER;  
File for Sandoz’ 351(k) application, BLA 761042 referencing Enbrel (etanercept).

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARLENE T SCHULTZ-DEPALO

09/17/2015

Memo entered into DARRTS on behalf of the CDER Exclusivity Board

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # BLA # 761042	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Erelzi Established/Proper Name: GP2015 (proposed biosimilar to Enbrel) Dosage Form: Injectable		Applicant: Sandoz Inc. Agent for Applicant (if applicable):
RPM: Jessica Lee		Division: DPARP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)  BLA Application Type: <input checked="" type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>August 30, 2016</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only):  
 (*confirm chemical classification at time of approval*)

- |   |   |
|---|---|
| <input type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation          | <input type="checkbox"/> Direct-to-OTC            |
| <input type="checkbox"/> Breakthrough Therapy designation |   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)  
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR  
 Submitted in response to a PMC  
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)  
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS:  MedGuide  
 Communication Plan  
 ETASU  
 MedGuide w/o REMS  
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

<b>Action Letters</b>	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) APP 8/30/16
<b>Labeling</b>	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>Review(s) <i>(indicate date(s))</i></li> </ul>	2/16/16; 10/26/15 2/12/16; 10/26/15
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 9/29/15 DMEPA: <input type="checkbox"/> None 8/24/16; 7/21/16 DMPP/PLT (DRISK): <input type="checkbox"/> None 8/10/16 OPDP: <input type="checkbox"/> None 8/5/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None 8/30/16 Other: <input type="checkbox"/> None 8/29/16
<b>Administrative / Regulatory Documents</b>	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	9/29/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i>	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>March 9, 2016</u> If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	8/25/16; 8/24/16 (2); 8/16/16; 8/12/16; 7/29/16; 7/25/16; 7/18/16;6/17/16; 6/9/16; 5/19/16; 5/2/16; 4/29/16; 4/15/16;4/8/16 (2); 4/4/16; 3/31/16; 3/18/16; 3/10/16 (2); 3/8/16; 2/26/16; 2/22/16; 1/29/16; 12/18/15; 12/15/15; 12/11/16; 12/2/15; 11/19/16; 11/10/15; 10/9/15; 10/2/15; 9/28/15; 9/17/15; 8/19/15
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	6/17/16; 1/16/13

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	July 13, 2016
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/29/16
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 8/29/16
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 8/25/16
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	7/28/16
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	7/28/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> ) <sup>5</sup>	<input type="checkbox"/> None DDDP 9/14/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 6/15/16; 6/14/16; 6/2/16 (2); 5/20/16
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/28/16; 9/11/15

<sup>5</sup> For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see “Section 508 Compliant Documents: Process for Regulatory Project Managers” located in the CST electronic repository).

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/25/16; 9/22/15
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested 2/12/16; 2/8/16; 1/19/16
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 8/5/16
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/12/16; 4/29/16; 9/15/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews <sup>6</sup>	
• Tertiary review <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/12/16
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/12/16; 9/24/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None 8/4/16; 7/29/16; 7/26/16
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	8/12/16
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

<sup>6</sup> Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JESSICA K LEE  
08/30/2016



BLA 761042

**GENERAL ADVICE**

Sandoz, Inc.  
Attention: Zhengui Liu, Ph.D.  
Manager Regulatory Affairs  
US Biopharmaceuticals  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Lui:

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for GP2015.

We also refer to your July 28, 2016, submission, containing your request for review of the proposed suffixes for the nonproprietary name of your proposed product.

We have reviewed the submission and have the following comments:

1. We find your proposed nonproprietary name, etanercept- (b) (4) unacceptable as the proposed suffix “- (b) (4) presents certain risk for errors due to the inclusion of letters that represent common medical abbreviations and terms ( (b) (4) as abbreviation for (b) (4) , and (b) (4) may be an abbreviation for (b) (4) )<sup>1</sup>. Additionally, the suffix is composed of the letters (b) (4) that are the (b) (4) common to and appear in the same order as (b) (4)”, and thus this suffix is not (b) (4) .
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.

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<sup>1</sup> Neil M Davis, *Medical Abbreviations: 30,000 Conveniences at the Expense of Communication and Safety*. Pennsylvania, 2009

If you have any questions regarding the contents of this letter or any other aspects of the proper name review process, contact Michael Sinks at (240) 402-2684. For any other questions regarding this application, contact Jessica Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Office of Medication Error Prevention and Risk  
Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KELLIE A TAYLOR  
08/25/2016



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation II

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**ELECTRONIC CORRESPONDENCE**

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**DATE:** August 24, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	<b>From:</b> Jessica Lee, PharmD Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b>	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3769

**Subject:** BLA 761042 (GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept))  
Labeling for Carton and Container

**Total no. of pages including cover:**

**Comments:** Please confirm receipt.

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**Document to be mailed:**                      YES                      xNO

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Dear Dr. Liu,

Your submission dated, July 30, 2015, is currently under review. We have the following comments regarding your proposed container labels and carton labeling submitted via email on August 18, 2016:

**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).

**Carton Labeling (Prefilled syringe 1-count: 25 mg/0.5 mL and 50 mg/mL)**

3. 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.

**Container Label (Prefilled syringe: 25 mg/0.5 mL and 50 mg/mL)**

4. 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.

Be advised that these labeling changes are not necessarily the Agency’s final recommendations and that additional labeling changes may be forthcoming as we continue to review the label.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the BLA by August 26, 2016. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov), followed by an official submission to the BLA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: JAbdus-Samad 8/24/16  
JLee 8/24/16

Initialed by: SBarnes 8/24/16

Finalized by: JLee 8/24/16

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/s/

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JESSICA K LEE  
08/24/2016



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation II

**ELECTRONIC CORRESPONDENCE**

**DATE:** August 24, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	<b>From:</b> Jessica Lee, PharmD Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b>	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3769

**Subject:** BLA 761042 (GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept))  
Labeling

**Total no. of pages including cover:**

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Dear Dr. Liu,

Your submission dated, July 30, 2015, is currently under review. Attached are our revisions to your proposed package insert (PI), Medication Guide, and Instructions for Use. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the label.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the BLA by August 26, 2016. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov), followed by an official submission to the BLA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: JLee 8/23/16

Initialed by: SBarnes 8/23/16  
TBBS 8/23/16  
OCC 8/24/16  
SYim 8/24/16

Finalized by: JLee 8/24/16

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

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/s/

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JESSICA K LEE  
08/24/2016



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** August 16, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Jessica Lee, PharmD <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
 Information Request for PMR/PMC

**Total no. of pages including  
 cover:**

**Comments:**

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Dear Dr. Liu,

We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following requirements for Postmarketing Requirement (PMR) and Postmarketing Commitments (PMC):

**Postmarketing Requirement (PMR):**

1. Develop a presentation that can be used to accurately administer etanercept-xxxx to pediatric patients who weigh less than 63 kg.

Final Report Submission: 12/31/2019

**Postmarketing Commitments (PMC):**

2. 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 method final validation report and the release and stability acceptance criteria as a Prior Approval Supplement.

Final Report Submission: 12/31/2017

3. 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 Changes Being Effected in 30 days (CBE30) and include any change in filtration parameters based upon the study.

Final Report Submission: 9/30/2017

4. Use a validated method to measure break loose, glide force (BLGF) for (b) (4) drug product pre-filled syringes to generate data from commercial batches to define release specifications for BLGF. Submit the study report and specifications for BLGF in the annual report.

Final Report Submission: MM/DD/YYYY

5. Develop methods for confirming the injection depth (e.g. needle length exposed for injection), audible feedback (e.g. occurrence of second click), and visual feedback (e.g. plunger fills the window and stops moving) for release testing. Define release specifications that meet design output specifications for injection depth, audible feedback, and visual feedback for lot release testing prior to launch of Erelzi. Submit the study report and release specifications in the annual report.

Final Report Submission:

MM/DD/YYYY

6. Complete transport validation testing to assess mechanical stress on the new folding box and transport carton prior to launch of Erelzi. Submit the final transport validation report.

Final Report Submission:

MM/DD/YYYY

Provide your agreements and/or revisions along with proposed timelines for completion by August 18, 2016. The information can be sent by email to Jessica Lee at [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov). Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Jessica Lee, Senior Regulatory Program Manager, at 301-796-3769.

Drafted by: JLee 8/3/16

Initialed by: SBarnes 8/3/16  
TBBS 8/15/16  
MShapiro 8/3/16  
SMollo 8/4/16  
NNikolov 8/3/16  
SSeymour 8/4/16; 8/16/16  
OCC (SVaid) 8/15/16  
ORP (JSitlani) 8/15/16

Finalized by: JLee 8/16/16

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/s/  
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JESSICA K LEE  
08/16/2016



**Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Drug Evaluation ODEII**

**FACSIMILE TRANSMITTAL SHEET**

DATE: August 12, 2016

To: Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	From: CDR Sadaf Nabavian Regulatory Project Manager
Company: Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
Fax number: NA	Fax number: 301-796-9718
Phone number: 609-627-8679	Phone number: 301-796-2777
Subject: BLA 761024 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept)) Labeling	

Total no. of pages including cover: 60

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BLA 761042  
GP2015 (a proposed biosimilar to Enbrel)  
Sandoz, Inc.

Dear Dr. Liu:

Your 351(k) Biologics License Application (BLA) 761042, submitted on July 30, 2015, is currently under review. We are providing labeling comments pertaining to the carton/container label noted below. We are also providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

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. We recommend following the approach described in 21 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. Revise the nonproprietary name from “(\*etanercept)” to “(\*etanercept-xxxx\*\*).”
4. Revise the strength (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. Note the presentation of “25 mg/0.5 mL” is correct.
5. Increase the prominence of the route of administration statement by bolding.
6. As currently presented in your proposed labels and labeling, you have used (b) (4) color blocking overlaid by (b) (4) font for the 25 mg/0.5 mL strength and (b) (4) color blocking overlaid by (b) (4) font for the 50 mg/mL strength. However, because the color scheme is (b) (4) of the reference product, US-licensed Enbrel, and practitioners are accustomed to the US-licensed Enbrel display, the presentation of the strength statements may be a source of confusion and possible wrong strength errors could be committed. We recommend that you either (b) (4) of the reference product US-licensed Enbrel or (b) (4) to US-licensed Enbrel.

B. Container Label (Prefilled syringe: 25 mg/0.5 mL and 50 mg/mL)

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\* FDA is using the descriptor “GP2015\*” in place of the nonproprietary name because the nonproprietary name for Erelzi has not been determined. GP2015 is not intended to be included in your final printed labels and labeling.

\*\*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 your final printed labels and labeling.

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. Container Label (Pen: (b) (4) 50 mg/mL)

1. 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

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

D. Foil Labeling (Prefilled Syringe: 25 mg/0.5 mL and 50 mg/mL)

1. 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

E. Carton labeling (All package sizes; Prefilled syringe: 25 mg/0.5 mL and 50 mg/mL; Sensoready Pen)

1. On the principal display panel, revise the statement (b) (4) to read “Must be refrigerated”.
2. Consider revising the schematic image of the PFS and Pen by utilizing a more accurate image or photo of the PFS or Pen.
3. The carton labeling lacks room temperature storage instructions and a method for end-users (patients/caregivers) to track when they removed the product from refrigerator storage. Revise the storage instructions on the back panel to provide instructions for patients/caregivers. For example:

**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.

(b) (4) date removed from the refrigerator \_\_\_/\_\_\_/\_\_\_.

4. 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 50 mg etanercept-xxxx, citric acid (0.786 mg), L-lysine HCl (4.6 mg), sodium chloride (1.5 mg), sodium citrate (13.52 mg), sucrose (10 mg), hydrochloric acid and sodium hydroxide to adjust pH, Water for Injection, USP.

a. Note deletion of trailing zeros (e.g. 4.60 mg to 4.6 mg) within the list of ingredients.

b. Ensure the listing of ingredients on the carton labeling is consistent with the *Description and Composition of the Drug Product* submitted in the BLA and the PI section 11. For example, there is inconsistency between names of ingredients (b) (4) vs. sodium citrate, (b) (4) vs. L-lysine).

Submit revised labeling incorporating the recommendations listed above and in the attached marked-up label via email to [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov) by the close of business on Thursday, August 18, 2016, followed by an official submission to the BLA. If there are any questions, contact Jessica Lee, Sr. Regulatory Project Manager, at 301-796-3769.

Drafted by: SNabavian/8.12.2016

Cleared by: LJafari/8.12.2016

Finalized by: SNabavian/8.12.2016

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/s/  
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SADAF NABAVIAN  
08/12/2016

## Harris, Sarah

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**From:** Liu, Zhengyu <zhengyu.liu@sandoz.com>  
**Sent:** Thursday, August 11, 2016 11:28 AM  
**To:** Harris, Sarah  
**Cc:** Sinks, Michael  
**Subject:** RE: revise preference order of list of suffix for GP2015 RE: BLA 761042: Suffixes

**Sensitivity:** Confidential

**Categories:** DPARP

Thank you Sarah. Have a good day.

Best regards, eddy

**Zhengyu (eddy) Liu, Ph.D., RAC**  
Regulatory Affairs  
US Biopharmaceuticals, Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540  
USA

Phone +1 609 6278679  
Cell +1 (b) (6)  
Fax +1 609 6278659  
[zhengyu.liu@sandoz.com](mailto:zhengyu.liu@sandoz.com)  
[www.novartis.com](http://www.novartis.com)

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**From:** Harris, Sarah [mailto:Sarah.Harris@fda.hhs.gov]  
**Sent:** Thursday, August 11, 2016 11:26 AM  
**To:** Liu, Zhengyu <zhengyu.liu@sandoz.com>  
**Cc:** Sinks, Michael <Michael.Sinks@fda.hhs.gov>  
**Subject:** RE: revise preference order of list of suffix for GP2015 RE: BLA 761042: Suffixes  
**Sensitivity:** Confidential

Hi Eddy,

Thank you for your call and follow up email. FDA is still reviewing the proposed suffixes. I do not further updates to share at this time. I have distributed your new order of preferences to the team.

Kind Regards,  
Sarah

Sarah Harris, PharmD  
Safety Regulatory Project Manager | Team Leader (Acting) | OSE | CDER | FDA  
[sarah.harris@fda.hhs.gov](mailto:sarah.harris@fda.hhs.gov) | 240.402.4774

---

**From:** Liu, Zhengyu [mailto:zhengyu.liu@sandoz.com]  
**Sent:** Thursday, August 11, 2016 9:32 AM  
**To:** Harris, Sarah

**Cc:** Sinks, Michael

**Subject:** revise preference order of list of suffix for GP2015 RE: BLA 761042: Suffixes

**Sensitivity:** Confidential

Good Morning Sarah,

I left you a voice mail and wanted to touch base with you on the review status of the GP2015 INN suffix list proposed by Sandoz. Meanwhile Sandoz wants to revise our preference order of the four suffixes after conducting additional studies. We are flipping the preference order of #2 and #3, and therefore the list of suffixes in order of our preference now becomes:

1. (b) (4)
2. sZZS
3. (b) (4)
4. [REDACTED]

We will submit it formally to eCTD on Friday. We are looking forward to the FDA's feedback. Thank you.

**Best regards, eddy**

**Zhengyu (eddy) Liu, Ph.D., RAC**

Regulatory Affairs  
US Biopharmaceuticals, Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540  
USA

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Cell +1 (b) (6)  
Fax +1 609 6278659  
[zhengyu.liu@sandoz.com](mailto:zhengyu.liu@sandoz.com)  
[www.novartis.com](http://www.novartis.com)

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**From:** Harris, Sarah [<mailto:Sarah.Harris@fda.hhs.gov>]

**Sent:** Friday, August 05, 2016 3:22 PM

**To:** Joy, Jordanis <[jordanis.joy@sandoz.com](mailto:jordanis.joy@sandoz.com)>

**Cc:** Lee, Jessica K (ODEII/DPARP) <[Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov)>; Sinks, Michael <[Michael.Sinks@fda.hhs.gov](mailto:Michael.Sinks@fda.hhs.gov)>; Liu, Zhengyu <[zhengyu.liu@sandoz.com](mailto:zhengyu.liu@sandoz.com)>

**Subject:** RE: BLA 761042: Suffixes

**Sensitivity:** Confidential

Good Afternoon Jordanis,

Thank you for the proposals below. I have distributed them to the team for review.

Please be sure to follow up with an official submission to the BLA as well.

Kind Regards,  
Sarah

Sarah Harris, PharmD  
Safety Regulatory Project Manager | Team Leader (Acting) | OSE | CDER | FDA  
[sarah.harris@fda.hhs.gov](mailto:sarah.harris@fda.hhs.gov) | 240.402.4774

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**From:** Joy, Jordanis [<mailto:jordanis.joy@sandoz.com>]  
**Sent:** Friday, August 05, 2016 1:52 PM  
**To:** Harris, Sarah  
**Cc:** Lee, Jessica K (ODEII/DPARP); Sinks, Michael; Liu, Zhengyu  
**Subject:** BLA 761042: Suffixes  
**Importance:** High

Good Afternoon Sarah,

I hope this email finds you well. Sandoz really appreciates FDA's advice and collaboration during yesterday's teleconference regarding the suffix to accompany Sandoz' biosimilar etanercept product.

A large number of potential suffixes were generated by internal discussions within Sandoz as well as in consultation with both a creative branding agency and a brand name agency. Sandoz conducted a series of analyses on the potential suffixes to evaluate whether they had meaning as individual words or could be confused with established abbreviations that are associated with meaning. For all potential suffixes, analyses were conducted on both the full four letter constructs as well as on the first three letters of each potential suffix.

The following evaluations were made by both Sandoz staff and an external brand name agency:

1. An internet check using google.com and bing.com
2. An abbreviation check by use of abbreviations.com and a check of proprietary name databases
3. A safety check conducted by drug safety experts
4. A trademark check conducted by legal professionals.
5. A phonetic check by an external brand name agency

Based on the above analyses, we are providing the FDA with the following four options for consideration as suffixes to the proper name of the Sandoz biosimilar etanercept product.

1. (b) (4)
2. (b) (4)
3. sZZs
4. (b) (4)

These potential suffixes are provided in order of our preference. We are conducting additional analyses that will be completed next week. It is possible that Sandoz may revise the priority order of the proposed suffixes based on the additional analyses as discussed in the teleconference yesterday.

We are looking forward to the FDA's feedback, and if you have any questions, feel free to contact me at any time.

Thank you and have a great weekend!

Kind Regards,  
Jordanis

**Jordanis Joy, PharmD.**  
Biopharmaceutical Regulatory Affairs  
Sandoz Inc., a Novartis division  
100 College Road West  
Princeton, NJ 08540, USA

Office : +1 609-720-6641

Cell : +1 [REDACTED] (b) (6)

[jordanis.joy@sandoz.com](mailto:jordanis.joy@sandoz.com)



Learn more about biosimilars @ [www.sandoz-biosimilars.com](http://www.sandoz-biosimilars.com)

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/s/  
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SARAH J HARRIS  
08/11/2016



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation II

**ELECTRONIC CORRESPONDENCE**

**DATE:** July 29, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	<b>From:</b> Jessica Lee, PharmD Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b>	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3769

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Labeling

**Total no. of pages including cover:**

**Comments:** Please confirm receipt.

**Document to be mailed:**                      YES                      xNO

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Dear Dr. Liu,

Your submission dated, July 30, 2015, is currently under review. Attached are our revisions to your proposed package insert (PI), Medication Guide, and Instructions for Use. Comments regarding some changes are embedded within the product label. The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as we continue to review the label.

Submit a clean copy and a tracked-change version of the label incorporating our recommended changes to the BLA by August 5, 2016. The information can be sent by electronic mail to [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov), followed by an official submission to the BLA. If you have any questions, please contact Jessica Lee, Regulatory Project Manager, at 301-796-3769.

Drafted by: JLee 7/26/16

Initialed by: TBBS 7/25/16  
SBarnes 7/26/16  
OCC 7/28/16  
NNikolov 7/28/16

Finalized by: JLee 7/29/16

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/s/  
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JESSICA K LEE  
07/29/2016



BLA 761042

INFORMATION REQUEST

Sandoz, Inc.  
Attention: Zhengyu Liu, Ph.D.  
Manager, U.S. Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your original Biologics License Application received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015.

We are reviewing your submission and have the following comments related to the Drug Product (DP) specifications for GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept). We request a prompt written response in order to continue our evaluation. Please submit your response prior to August 1, 2016.

**Release specifications / Shelf life specification:**

1. The release specifications for some GP2015 drug product methods are too broad based on data from release and stability testing. The following release specifications should be tightened or an appropriate scientific justification may be provided.
  - a. For Size Exclusion Chromatography (SEC), the release specifications are main peak purity  $\geq$  (b) (4)%, sum of HMW  $\leq$  (b) (4)% and sum of LMW %  $\leq$  (b) (4)%. The justification for these criteria is based on the ANOCOVA calculation, which incorporates an offset based on stability data. For example, for HMW species you conclude that a release specification of (b) (4)% supports a shelf life of (b) (4) months assuming storage at (b) (4) (b) (4). However, we note that your actual release data are all  $\leq$  (b) (4)% and at Condition A, the data are  $\leq$  (b) (4)%. Given the uncertainty of the storage conditions when GP2015 will be in the hands of patients, we are concerned that any GP2015 drug product lots that contain (b) (4)% HMW species at release, could potentially have  $>$  (b) (4)% HMW species at the time of patient use. We recommend tightening the release criteria for main peak, HMW and LMW species based on your actual results that would provide an additional cushion for lots that may be used by patients near

the end of their shelf life. Note that you should reconsider the release and stability criteria for GP2015 drug substance.

- b. We have similar concerns for acidic variants by Capillary Zone electrophoresis. We recommend tightening the release criteria for acidic variants based on your actual results that would provide an additional cushion for lots that may be used by patients near the end of their shelf life. Note that you should reconsider the release and stability criteria for GP2015 drug substance.
  - c. The release criteria for osmolality should include an upper limit as well as a lower limit.
  - d. Provide an additional explanation for the change to the lower limit for content for the End of Shelf Life specification (from (b) (4) ng/mL at release to (b) (4) mg/mL at EoSL). It may be acceptable to have a lower limit to account for the potential loss of protein during its shelf life, however, your stability data do not show any appreciable loss in content over 36 months.
2. For GP2015 drug product stability testing, you should assess potency at every time point and not just annually.
  3. We note for GP20015 drug substance, you include a release test for density, which is needed for determining content and for the appropriate dilution of drug substance during the manufacture of GP2015 drug product. However, we note that your acceptance criterion is "Report value". You did not provide an adequate justification for "Report value" and it is not clear why a quantitative range cannot be established. Establish a quantitative acceptance criterion, provide additional justification or alternatively, you could consider testing for density to be an in-process test with appropriate limits.
  4. Regarding the implementation of the Reversed Phase Chromatography method as a release and stability test for GP2015 drug substance and drug product, we note your proposal to implement this method in your submission dated April 15, 2016. Provide a time frame by which this method can be implemented. The implementation of this method can be a Post Marketing Commitment.

If you have any questions, please contact me at 301-796-0962 or [keith.olin@fda.hhs.gov](mailto:keith.olin@fda.hhs.gov).

Sincerely,

Keith J. Olin -S

Digitally signed by Keith J. Olin -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Keith J. Olin -S,  
0.9.2342.19200300.100.1.1=1300214407  
Date: 2016.07.25 17:20:52 -04'00'

CDR Keith Olin, Pharm.D.  
United States Public Health Service  
Senior Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



BLA 761042

**GENERAL ADVICE**

Sandoz, Inc.  
Attention: Zhengui Liu, Ph.D.  
Manager Regulatory Affairs  
US Biopharmaceuticals  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your Biologic Licensing Application (BLA) 761042, submitted under section 351(k) of the Public Health Service Act, on July 30, 2015.

We note that your submission does not include a distinguishing identifier in the proper name of your product. FDA requests that Sandoz submit 3 proposed suffixes, listed in your order of preference, composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at such time as Sandoz's proposed biosimilar to Enbrel may be licensed. Your proposed suffixes should be devoid of meaning and follow the recommendations for proposed suffixes in Section V of FDA's draft guidance on Nonproprietary Naming of Biological Products (see <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>).

In addition, given that FDA has requested comment in the Notice of Availability for the draft guidance (80 FR 52296, August 28, 2015) on, among other things, the potential benefits and challenges of designating a suffix in the proper name of a biological product that is devoid of meaning versus meaningful (e.g., a suffix derived from the name of the license holder), Sandoz also may consider requesting FDA review of (b) (4) or this product, or proposing 3 additional suffixes that are meaningful (e.g., derived from the name of the prospective license holder) and composed of four lowercase letters. Any additional suffixes proposed should be listed in your order of preference in your submission, and will be evaluated in parallel to any suffixes you propose that are devoid of meaning.

We encourage Sandoz to respond to the information request no later than July 30, 2016. You may include with your submission any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in the draft guidance. FDA will notify Sandoz upon completion of the Agency's evaluation.

If you have any questions regarding the contents of this letter or any other aspects of the proper name review process, contact Michael Sinks at 240-402-2684. For any other questions regarding this application, contact Jessica Lee, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3769.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH  
Deputy Director  
Office of Medication Error Prevention and Risk  
Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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KELLIE A TAYLOR  
07/18/2016



BLA 761042

**INFORMATION REQUEST**

Sandoz, Inc.  
Attention: Zhengyu Liu, Ph.D.  
Manager, U.S. Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your original Biologics License Application received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015.

We are reviewing your submission and have the following comments related to the Drug Product (DP) of GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept). We request a prompt written response in order to continue our evaluation. Please submit your response prior to June 24, 2016.

**Product Quality Microbiology – Drug Product**

1. With regard to the bacterial retention studies, PDA Technical Report No. 26, Chapter 6.8.3 suggests removing the bactericidal component or using a surrogate fluid, however, it does not suggest the use of (b)(4). We maintain that the use of (b)(4) in place of the product for the challenge organism preparation is not acceptable. A surrogate fluid which matches the drug product as much as possible in terms of its physical and chemical characteristics should be used for the challenge study. Please repeat the bacterial retention study using a surrogate fluid that more closely resembles the composition of GP2015 drug product. Also, please inform the Agency when you expect to complete the study. If necessary, the study may be completed as a Post-Marketing commitment.
2. As part of the validation of the Rapid Sterility Test, a bioluminescent background test was completed and results from the test using GP2015 DP without spiking were provided. However, the results from the positive control, verifying that the bioluminescence reaction is not inhibited by the DP were not provided. Please provide results from the positive control (described in section 3.2.P.5.3.2.2.4.3 Verification That Bioluminescence Reaction Is Not Inhibited).

3. Please provide the specific conditions under which the alternative sterility test method would be used and amend the BLA accordingly. Also, please confirm that the alternative test method will not be used in response to a sterility test failure

If you have any questions, please contact me at 301-796-0962 or [keith.olin@fda.hhs.gov](mailto:keith.olin@fda.hhs.gov).

Sincerely,

Keith J. Olin -S

Digitally signed by Keith J. Olin -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Keith J. Olin -S,  
0.9.2342.19200300.100.1.1=1300214407  
Date: 2016.06.17 16:27:16 -0400

CDR Keith Olin, Pharm.D.  
United States Public Health Service  
Senior Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



IND 114187

**MEETING MINUTES**

Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540

Attention: Zhengyu (Eddy) Liu, Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Liu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GP2015.

We also refer to the telecon between representatives of your firm and the FDA on May 18, 2016. The purpose of the meeting was to discuss the development of a (b) (4) dosage form for GP2015, a proposed biosimilar to US-licensed Enbrel.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Biosimilar Product Development  
**Meeting Category:** Biosimilar Biologic Product Development (BPD) Type 2  
**Meeting Date and Time:** May 18, 2016 from 3:00 – 4:00 PM, EST  
**Meeting Location:** Teleconference  
**Application Number:** IND 114187  
**Product Name:** GP2015  
**Indication:** GP2015 is being developed for the same indications as approved for US-licensed Enbrel  
**Sponsor Name:** Sandoz  
**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Leila P. Hann

**FDA ATTENDEES**

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Sarah Yim, MD, Supervisory Associate Director, DPARP  
Nikolay Nikolov, MD, Clinical Team Leader, DPARP  
Rachel Glaser, MD, Clinical Reviewer, DPARP  
Marjorie Shapiro, PhD, Supervisory Biologist, Division of Biotechnology Review and Research I  
Peter Adams, PhD, Biologist, Division of Biotechnology Review and Research I  
Ping Ji, PhD, Clinical Pharmacologist Team Lead, Division of Clinical Pharmacology II  
Lei He, PhD, Clinical Pharmacologist, Division of Clinical Pharmacology II  
Greg Levin, PhD, Lead Mathematical Statistician, Division of Biometrics II  
Leila Hann, Senior Regulatory Project Manager, DPARP  
Sue Lim, M.D., Medical Officer, Therapeutic Biologic and Biosimilars Staff (TBBS)  
Carla Lankford, M.D., Ph.D. Science Policy Analyst, TBBS  
Kellie Taylor, Pharm. D., Deputy Director, Office of Medication Error Prevention and Risk Management (OMEPRM)  
Carlos Mena-Grillasca, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)  
Mishale Mistry, Pharm. D., Acting Team Leader, DMEPA  
Lubna Merchant, Pharm. D., Deputy Director, DMEPA  
CDR Irene Chan, Pharm. D., Deputy Director, DMEPA  
QuynhNhu Nguyen, M.S., Acting Associate Director for Human Factors, DMEPA

## **SPONSOR ATTENDEES**

Cindy Cao, Head and Executive Director, Regulatory Affairs Biopharmaceuticals  
Zhengyu Liu, US Regulatory Affairs Biopharmaceuticals  
Anthony Maffia, Vice President US Regulatory Affairs Biopharmaceuticals  
Carlos Sattler, Vice President Clinical Development and Medical Affairs

Mark McCamish, Global Head Biopharmaceutical & Oncology Injectables Development  
Malte Peters, Global Head Clinical Development Biopharmaceuticals  
Ingrid Schwarzenberger, Global Head Regulatory Affairs Biopharmaceuticals  
Wolfgang Fischer, Global Head Project Management  
Guido Wuerth, Global Program Medical Director  
Oliver von Richter, Global Clinical Pharmacology Manager  
Christine Berndt, Global Program Leader  
Iris Birnkammer, Global Program Manager  
Gerard Linnane, Head Global Device Development  
Violeta Gabrijelcic, Head Global Pharmaceutical & Device Development  
Peter Alliger, Technical Project Leader  
Andrej Artenjak, Scientist Analytical Projects  
Martin Müller, Associate Scientist, Pharmaceutical Development  
Elisabeth Kapeller, Senior Manager Regulatory Device Group  
Fritz Reiter, Team Leader Regulatory CMC  
Bianca Targosz, Associate Manager Regulatory CMC  
Bettina Mayer, Regulatory Team Leader  
Mauro Sergi, Group Head, Pharmaceutical Development

## **1.0 BACKGROUND**

Sandoz, Inc. previously met with DPARP and DDDP on July 9, and December 19, 2012. A meeting request was received March 01, 2016 which was granted March 16, 2016. A teleconference was held May 18, 2016.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by Sandoz and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

FDA sent Preliminary Comments to Sandoz on May 17, 2016, and Sandoz provided a presentation to the FDA on May 18, 2016.

## **2.0 DISCUSSION**

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**Discussion:** See Discussion of Questions 2 and 3.

**FDA Response Question 4c:** We do not agree at this time. See FDA Response to Question 2 above.

**Discussion:** See Discussion of Questions 2 and 3.

### **3.0 PREA REQUIREMENTS**

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355c)], all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(m) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable

with the reference product is considered to have a new "active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived or deferred.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (PSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed PSP prior to initiating your comparative clinical study (see additional comments below regarding expected review timelines).

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an initial PSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the initial PSP. The initial PSP must include an outline of the pediatric study or studies that a sponsor plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); and any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive initial PSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.11 in FDA's guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the initial PSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by FDASIA (see section 505B(e) of the FD&C Act and FDA's Guidance for Industry on Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>). It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

#### **4.0 DATA STANDARDS FOR STUDIES**

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team ([cder-edata@fda.hhs.gov](mailto:cder-edata@fda.hhs.gov)) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

## **5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS**

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting

mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

## **6.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues requiring further discussion were identified during the meeting.

## **7.0 ACTION ITEMS**

No action items were identified during the meeting.

## **8.0 ATTACHMENTS AND HANDOUTS**

Sandoz's presentation received May 18, 2016 which was referenced during the teleconference is attached below.

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/s/  
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LEILA P HANN  
06/17/2016



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** June 09, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Leila P. Hann <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-2300. Thank you.

We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following comments and request for response:

No cases of anaphylaxis have been reported in the clinical studies. Clarify if cases of anaphylaxis have occurred in the GP2015 clinical development program and whether these were classified using the definitions by Sampson et al (Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. *J Allergy Clin Immunol* 2006; 117(2):391-97). If not, we request that you retrospectively identify cases using the NIAID/FAAN criteria.

Provide a response by email (Jessica.Lee@fda.hhs.gov) or facsimile (301-796-9728), by 3pm, EST on Tuesday, June 14, 2016. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ June 07, 2016  
Cleared: R. Glaser/ June 07, 2016  
N. Nikolov/ June 07, 2016  
TBBS/ June 09, 2016  
S. Barnes/ June 09, 2016  
Finalized: L. Hann/ June 09, 2016

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/s/  
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LEILA P HANN  
06/09/2016



BLA 761042

**INFORMATION REQUEST**

Sandoz Inc.  
Attention: Zhengyu Liu, Ph.D.  
Manager, US Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your Biologics License Application (BLA) dated and received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for Brelvina (etanercept) 50 mg/mL and 25 mg/0.5mL Injection.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by June 3, 2016 in order to continue our evaluation of your BLA.

**Product Quality Microbiology – Drug Product**

1. Bacterial retention studies completed to validate the sterilizing filter were not adequately performed. The use of (b) (4) in place of the product for the challenge organism preparation is not acceptable. A surrogate fluid which matches the product as much as possible in terms of its physical and chemical characteristics should be used for the challenge study. Alternatively, the bactericidal effect of the formulated drug product may be overcome by performing the study at a reduced exposure time, or using modified process or using a modified product, etc. Propose a strategy and timeframe for repeating the study with more relevant challenge conditions.
2. With regard to the two sterility test methods proposed for release testing, the BLA states that the rapid sterility test is (b) (4) and that the compendial sterility test method (b) (4). (b) (4). The Applicant should test for sterility using one method.
3. In addition, the rapid test has not been adequately validated. A full validation study supporting the use of this method should be submitted. More robust studies are necessary to determine the limit of detection. In addition, the bioluminescent background test should be performed using the appropriate controls.

4. The description of the microbial ingress test in Section 3.2.P.2 Pharmaceutical Development states that the two controls included in the study were breached with (b) (4)  $\mu\text{m}$  capillary tubes. In addition, it states the limit of detection (LOD) was determined to be (b) (4)  $\mu\text{m}$ .  
A breach size of (b) (4)  $\mu\text{m}$  is relatively large, therefore the test is inadequate. Please repeat the study using a smaller breach size in the positive control. Include a description of how the limit of detection is determined in this study and how it correlates with the LOD of the dye ingress test used to test drug product placed on stability.
5. With regard to the proposed in-process controls, please implement in-process endotoxin testing with appropriate limits to your microbial control strategy.
6. Provide the purpose of the container closure integrity test completed (b) (4) (b) (4) during process validation. No description was provided in the BLA.
7. With regard to the endotoxin test method, the effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin standard (CSE or RSE) into undiluted drug product and then testing for recoverable endotoxin over time. Please complete this study to demonstrate that drug product does not interfere with endotoxin recoverability and submit the study report to the BLA.

If you have any questions, please contact me, at (240) 402-2725.

Sincerely,

Maryam  
Kordbacheh  
changi -A

Digitally signed by Maryam  
Kordbachehchangi -A  
DN: c=US, o=U.S. Government,  
ou=HH5, ou=FDA, ou=People,  
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Date: 2016.05.19 15:46:21 -04'00'

Maryam Changi, Pharm.D.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operation  
Office of Product Quality  
Center for Drug Evaluation and Research

**From:** [Olin, Keith](#)  
**To:** "[Liu, Zhengyu](#)"  
**Cc:** [Hann, Leila](#); [Olin, Keith](#)  
**Subject:** BLA 761042 GP2015 - Information Request\_050216  
**Date:** Monday, May 02, 2016 9:56:05 AM

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Eddy,

Please refer to your original Biologics License Application received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015.

We are reviewing your submission and have the following comments related to the Drug Substance and Product Quality of GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept). We request a prompt written response in order to continue our evaluation. Please submit your response prior to May 6, 2016.

**Information Request:**

1. With regard to the response to question 1a submitted on April 22, 2016, please clarify if the action limits described in study protocol PV95.453 are the study acceptance criteria. In addition, endotoxin action and alert limits in the protocol are higher than the limits proposed in your response to Question 2 submitted March 22, 2016. Justify your proposed endotoxin limits.
2. With regard to response to question 1b submitted on April 22, 2016, please clarify if the action limits described in study protocol PV97.200 are the study acceptance criteria. In addition, clarify if the study will be conducted at the end of the (b) (4)

Please submit a response to me via email ([keith.olin@fda.hhs.gov](mailto:keith.olin@fda.hhs.gov)) and as well as submit your response officially to the BLA file.

Please confirm receipt.

Keith

Keith Olin, PharmD  
CDR, USPHS  
Office of Programs and Regulatory Operations  
Office of Pharmaceutical Quality/FDA  
301-796-0962



BLA 761042

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540

Attention: Zhengyu (Eddy) Liu, Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Liu:

Please refer to your Biologics License Application (BLA) dated July 30, 2015, submitted under section 351(k) of the Public Health Service Act for Erelzi (GP2015).

GP2015 is a proposed biosimilar to Enbrel (etanercept) (BLA 103795).

On April 28, 2016, we received your April 28, 2016, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is August 30, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “BIOSIMILAR BIOLOGICAL PRODUCT AUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FOR FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 29, 2016.

If you have any questions, call Leila P. Hann, Senior Regulatory Project Manager, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Sandra L. Barnes  
Chief, Project Management Staff  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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LEILA P HANN

04/29/2016

Signing on behalf of Sandra Barnes



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** April 15, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Leila P. Hann <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following comments and requests for response:

1. On March 18, 2016, the Agency requested documentation that the essential performance requirements have been included in the lot release specifications. Sandoz provided a summary of the lot release testing of (b) (4) GP2015\_50 in Table 13-2 of Module 3.2.R Technical summary (b) (4) device. The only functional performance 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. Include needle extension within the lot release criteria. Alternatively, provide a justification for why you do not consider the needle extension as essential performance requirement.
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. Sandoz' response on March 23, 2016 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. Sandoz further 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. Sandoz responded that the audible and visual feedback mechanisms have been verified as part of the Design Input Requirements; however, Sandoz does not plan to include the audible and visual feedback mechanisms with the lot release criteria. Your response on April 6, 2016 stated 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 Agency's position is injection time will affect the ability of the patient to receive the entire dose and injection time is not captured by dose accuracy testing. . Therefore, the Agency recommends that you include the audible and visual feedback mechanisms in lot release criteria.

Provide a response by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by 3pm, EST on Tuesday, March 19, 2016. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ April 13, 2016  
Cleared: S. Mollo/ April 14, 2016  
A. Stevens/ April 12, 2016  
TBBS/ April 14, 2016  
S. Barnes/ April 13, 2016  
Finalized: L. Hann/ April 15, 2016

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/s/  
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LEILA P HANN  
04/15/2016

**PeRC Meeting Minutes  
March 9, 2016**

**PeRC Members Attending:**

Lynne Yao

Hari Cheryl Sachs

Linda Lewis

Thomas Smith

Meshaun Payne

Michelle Roth-Kline

Wiley Chambers

George Greeley

Peter Starke (Did not review **Non Responsive**)

Dionna Green

Barbara Buch

Adrienne Hornatko-Munoz

Andrew Mulberg (Did not review **Non Responsive**, Erelzi, **Non Responsive**)

Lisa Faulcon (**Non Responsive** reviews only)

Raquel Tapia

John Alexander

Shrikant Pagay

Freda Cooner

Belinda Hayes

**Agenda**

9:00	Non Responsive				
9:15					
9:30					
9:45					
10:05					
10:20					
10:30					
10:40					
11:00					
11:10	BLA 761042	Erelzi (Biosimilar to Enbrel) Full Waiver/Partial/Deferral/Plan (with Agreed iPSP)	DPARP	Jessica Lee/Leila Hann	RA, pJIA, PsA, Ankylosing Spondylitis, Plaque Psoriasis
11:20	Non Responsive				
11:35					

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Non Responsive

**Erelzi (Biosimilar to Enbrel) Full Waiver/Partial/Deferral/Plan (with Agreed iPSP)**

- Proposed Indication: RA, pJIA, PsA, Ankylosing Spondylitis, Plaque Psoriasis
- The division noted that the pediatric plan presented for the NDA is consistent with the plan in the Agreed iPSP for the proposed indication.
- This product triggered PREA as a biosimilar product.
- The divisions agreed to the pediatric plan as it is the same plan as provided in the agreed iPSP. This includes a full waiver for plaque psoriasis due to safety concerns. These safety concerns will be provided in labeling of the biosimilar product. However, the division is planning to issue a PREA PMR to require the sponsor to develop an age-appropriate presentation to allow for accurate direct administration to patients with JIA.
- *PeRC Recommendations:*
  - The PeRC agreed with the division to grant a full waiver for PsA, AS, and Plaque psoriasis.

- PeRC recommends that a PREA PMR be issued for ages 2-17 years to develop an age appropriate presentation so that this product may be directly administered to pediatric patients down to 2 years of age with pJIA.

Non Responsive

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/s/  
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GEORGE E GREELEY  
04/13/2016



BLA 761042

**INFORMATION REQUEST**

Sandoz, Inc.  
Attention: Zhengyu Liu, Ph.D.  
Manager, U.S. Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your original Biologics License Application received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015.

We are reviewing your submission and have the following comments related to the Drug Substance and Product Quality of GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept). We request a prompt written response in order to continue our evaluation. Please submit your response prior to April 22, 2016.

**Information Request:  
Microbial Quality – Drug Substance**

1. Submit the following reports to the BLA:
  - a. Protocol for the small-scale study in support of microbial control of the proposed maximum <sup>(b) (4)</sup> hold times (amendment 0018, response to question 3).
  - b. Protocol (or acceptance criteria if the protocol is not available) for the studies to support microbial control of <sup>(b) (4)</sup> after sanitization and storage (amendment 0018, response to question 4).
2. Please amend the BLA to incorporate the following changes:
  - a. Bioburden limit of the <sup>(b) (4)</sup> CFU/ <sup>(b) (4)</sup> mL (amendment 0007, response to question 12.d).
  - b. Endotoxin <sup>(b) (4)</sup> limits (amendment 0018, response to question 2).
  - c. Endotoxin maximum valid dilution (MVD) for drug substance and <sup>(b) (4)</sup> (amendment 0007, response to question 18.a).

### Product Quality

3. Include the Reversed Phase Chromatography method as a release and stability test for GP2015 drug substance and drug product.
  - a. Update 3.2.S.4.1 Specification (Drug Substance) and 2.1.P.5.1 Specification (Drug Product) to include this method.
  - b. Update 3.2.S.4.2 Analytical Procedures (Drug Substance) and 2.1.P.5.2 Analytical Procedures (Drug Product) to include this method.
  - c. Update 3.2.S.4.3 Validation of Analytical Procedures (Drug Substance) and 2.1.P.5.3 Validation of Analytical Procedures (Drug Product) to include this method and submit the validation report to 3.2.R.
  - d. Update 3.2.S.4.5 Justification of Specifications (Drug Substance) and 2.1.P.5.5 Justification of Specifications (Drug Product) to include this method.
  - e. Update 3.2.S.7.2 Post-Approval Stability Protocol and Commitment (Drug Substance) and 3.2.P.8.2 Post-Approval Stability Protocol and Commitment (Drug Product) to include this method.

If you have any questions, please contact me at 301-796-0962 or [keith.olin@fda.hhs.gov](mailto:keith.olin@fda.hhs.gov).

Sincerely,

**Keith J. Olin -S**

Digitally signed by Keith J. Olin -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Keith J. Olin -S,  
0.9.2342.19200300.100.1.1=1300214407  
Date: 2016.04.08 16:58:58 -0400

CDR Keith Olin, Pharm.D.  
United States Public Health Service  
Senior Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** April 4, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Jessica Lee, PharmD <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following request for information:

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, you state the following:

*“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 audible and visual feedback mechanisms are not included within the essential performance requirements or lot release criteria. Include a requirement for the audible and visual feedback mechanisms of the autoinjector within the essential performance requirements and lot release specifications.

Submit the requested information by Wednesday, April 6, 2016. The information can be sent by email to Jessica Lee at [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov). Your response must also be submitted formally to the 351(k) BLA shortly thereafter. If you have any questions, please contact Jessica Lee, Senior Regulatory Program Manager, at 301-796-3769.

Drafted by: SMollo 3/29/16; 4/1/16  
JLee 3/30/16

Initialed by: SBarnes 3/30/16  
TBBS 3/30/16

Finalized by: JLee 4/4/16

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/s/  
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JESSICA K LEE  
04/04/2016

## Kord Bacheh Changi, Maryam

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**From:** Kord Bacheh Changi, Maryam  
**Sent:** Thursday, March 31, 2016 10:17 AM  
**To:** 'zhengyu.liu@sandoz.com'  
**Cc:** Hann, Leila; Olin, Keith  
**Subject:** CMC Information Request BLA 761042

**Importance:** High

Dear Mr. Liu,

We are reviewing the CMC portion of BLA 761042 and have the following information requests:

- During a recent FDA inspection of Sandoz GmbH - Schaftenau drug substance manufacturing facility in Langkampfen, Austria (FEI # 3004828473) for BLA 761042, our field investigators found that certain GP2015 drug substance and drug product stability data submitted in the BLA filing was generated by contract laboratories that are not listed in the submission. Provide updated information about all facilities used for the registration stability testing of both GP2015 drug substance and drug product. Update Sections 3.2.S.2.1 and 3.2.P.3.1 accordingly. Please note that FDA expectations on which facilities need to be identified in future New Drug Applications and Biologics License Applications were discussed at a regulatory meeting between Novartis Pharmaceuticals Corporation and Office of Process and Facilities (OPF) of FDA/CDER on December 15, 2015.

Please submit your responses as an amendment to your application. Please also submit a copy to me via email by close of business day on **April 7, 2016**.

Please kindly confirm the receipt of this email.

Thank you.

Maryam Changi, PharmD.  
RBPM, Office of Program and Regulatory Operations (OPRO)  
Office of Pharmaceutical Quality/CDER/FDA  
Phone:(240) 402-2725  
Email: [Maryam.Kordbachehchangi@fda.hhs.gov](mailto:Maryam.Kordbachehchangi@fda.hhs.gov)





Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** March 18, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Jessica Lee, PharmD <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:**

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following request for information:

1. A number of the essential performance requirements for the pre-filled syringe with needle safety device (PFS with NSD) and the autoinjector were located in a referenced document (i.e., Masterfile or 510k); however, the design requirements and specifications should be provided by the combination product sponsor under the BLA. Provide the essential performance requirements and related specifications for the PFS with NSD and the autoinjector under your 351(k) BLA. Provide a traceability matrix to the verification of these requirements. Please note that for the PFS with NSD the requirements for the NSD should be included (e.g., activation force, force to separate components, compression resistance), as well as the syringe (dose accuracy, needle length, break loose and glide force). Also, provide all of the essential performance requirements, specifications, and traceability to the verification of these requirements for the autoinjector. Please see below for an example on how to display this information. A table for each device (i.e. PFS with NSD and autoinjector is preferred).

Essential Performance Requirement	Specification	Verification

2. We note in the specifications for the autoinjector that the needle depth is (b) (4) mm and the injection time is up to (b) (4) seconds.
  - a. Provide a validation for the acceptability of the acceptance criteria of  $\leq$  (b) (4) seconds for the injection time of the autoinjector.
  - b. We are concerned that (b) (4) mm injection depth is not appropriate for the intended anatomical site. Provide a validation for the acceptability of this specification.
3. You have provided the GP2015\_PFS\_25\_50 in (b) (4) RMUEP for the pre-filled syringe with needle safety device, which is the Risk Management and Usability Plan. Please provide GP2015\_PFS\_25\_50 in (b) (4) RMUER, which is the Risk Management and Usability Report. The Agency expects the overall risk management activities, including

those completed by the device component manufacturer, to be contained within the BLA and approved by the BLA Applicant.

4. Although the submission includes in-process validation testing for the autoinjector, we were unable to locate the lot release testing requirements for the autoinjector. Provide documentation that the essential performance requirements have been included in the lot release specifications.

Provide a response by Wednesday, March 23, 2016. The information can be sent by email to Jessica Lee at [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov). Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Jessica Lee, Senior Regulatory Program Manager, at 301-796-3769.

Drafted by: SMollo 3/18/16  
JLee 3/18/16

Initialed by: SBarnes 3/18/16  
TBBS 3/18/16

Finalized by: JLee 3/18/16

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/s/

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JESSICA K LEE  
03/18/2016



BLA 761042

**INFORMATION REQUEST**

Sandoz, Inc.  
Attention: Zhengyu Liu, Ph.D.  
Manager, U.S. Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your original Biologics License Application received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept).

We are reviewing your submission and have the following comments related to the Drug Substance and Drug Product. We request a prompt written response in order to continue our evaluation. Please submit your response prior to March 31, 2016. If the data are not currently available, provide an estimate of when the data are likely to be submitted to the FDA.

**Information Request:**  
**Drug Substance**

1. 3.2.S.2.2 Description of the Manufacturing Process and Process Controls. The primary



2. 3.2.S.2.4 Controls of Critical Steps and Intermediates. We note that Tables 1-1 through 1-4 provide the operating parameters and in-process controls for the upstream and downstream manufacturing processes. Each of these parameters and in-process controls

is categorized as critical, key or non-key. We note that in 3.2.S.2.5 Process Validation, Tables 3-2, 3-4, 3-16 and 3-17, only show that critical process parameters and in-process controls were included in your validation studies. All process parameters, regardless of their classification as critical, key or non-key should be included in your validation studies. Furthermore, some of the acceptable ranges shown in 3.2.S.2.4 Tables 1-1 and 1-2 for key or non-key process parameters do not match the proven acceptable ranges shown in the process characterization studies (3.2.S.2.6.4 Process characterization) or some parameters classified as critical are not shown in Tables 1-1 or 1-2. Below are some specific examples of discrepancies, but the list does not show all the discrepancies between 3.2.S.2.4, 3.2.S.2.5 and 3.2.S.2.6. Provide updated information showing that the acceptable ranges for each process parameter studied in process characterization studies were included in the validation protocol. Also see comment #3.

a.

(b) (4)

b.

c.

3. 3.2.S.2.5 Process Validation and/or Evaluation.

- a. We note some discrepancies between the validated “acceptable range” shown in Table 3-16 “Critical Process Parameters” and the corresponding acceptable range for

that parameter shown in Table 1-3 in 3.2.P.2.4 Controls of Critical Steps and Intermediates, which represents your “expected conditions.” The acceptable ranges in Table 1-3 appear to be broader than the validated range. Narrow the acceptable ranges shown in Table 1-3 for the following parameters:

i.

ii.

iii.

(b) (4)

b.

c.

d.

(b) (4)

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8. 3.2.P.7 Container Closure System. Provide a description of the plunger rods used for assembly of the 25 mg/0.5 mL and 50 mg/1.0 mL PFS.

If you have any questions, please contact me at 301-796-0962 or [keith.olin@fda.hhs.gov](mailto:keith.olin@fda.hhs.gov).

Sincerely,

Keith J. Olin -S

Digitally signed by Keith J. Olin -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Keith J. Olin -S,  
0.9.2342.19200300.100.1.1=1300214407  
Date: 2016.03.10 16:51:57 -05'00'

CDR Keith Olin, Pharm.D.  
United States Public Health Service  
Senior Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



**Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: March 10, 2016**

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Jessica Lee, PharmD <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following request for information:

1. The Risk Estimation and Evaluation Report for the GP2015-<sup>(b) (4)</sup>50 that you provided on March 9, 2016 includes a table containing identified hazards; however, there is no information on how the hazards have been mitigated. In addition to identifying system hazards, the risk analysis should describe the mitigations that have been implemented to reduce the risk of those hazards and the effectiveness of the mitigation. Provide the documentation that includes the above information.
2. 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.

Submit the requested information by Friday, March 11, 2016. The information can be sent by email to Jessica Lee at [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov). Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Jessica Lee, Senior Regulatory Program Manager, at 301-796-3769.

Drafted by: SMollo 3/9/16  
JLee 3/9/16

Initialed by: SBarnes 3/9/16  
TBBS 3/10/16

Finalized by: JLee 3/10/16

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/s/  
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JESSICA K LEE  
03/10/2016



**Food and Drug Administration  
Center for Drug Evaluation and  
Research  
Office of Drug Evaluation II**

**FACSIMILE TRANSMITTAL SHEET**

**DATE: March 8, 2016**

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Jessica Lee, PharmD <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following request for information:

The Risk Management and Usability Engineering Report for the (b) (4) GP2015\_50 autoinjector references the 1) Risk Estimation and Evaluation Report (0154-010-RM-S003 (2.0)) and 2) Risk Management Report (b) (4) (0154-010-RM-S005 (1.0)) but we are unable to find the reports within the submission. Provide the location of these documents or submit these documents to the BLA.

Submit the requested information by Wednesday, March 9, 2016. The information can be sent by email to Jessica Lee at [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov). Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Jessica Lee, Senior Regulatory Program Manager, at 301-796-3769.

Drafted by: SMollo 3/8/16  
JLee 3/8/16

Initialed by: SBarnes 3/8/16  
TBBS 3/8/16

Finalized by: JLee 3/8/16

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/s/  
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JESSICA K LEE  
03/08/2016



BLA 761042

**INFORMATION REQUEST**

Sandoz, Inc.  
Attention: Zhengyu Liu, Ph.D.  
Manager, U.S. Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your original Biologics License Application received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept).

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation. Please submit your response prior to March 22, 2016. If the data are not currently available, provide an estimate of when the data are likely to be submitted to the FDA.

**Information Request:  
(Reference Sandoz, Inc. submission on December 11, 2015)**

**S.2.2 Description of the Manufacturing Process and Process Controls**

1. With regard to your response to question 11.a, it appears that the three [REDACTED] (b) (4) described in the amendment may not be sufficient to ensure microbial control of the manufacturing process because [REDACTED] (b) (4)

**S.2.4 Control of Critical Steps and Intermediates**

2. With regard to your response to question 12.e and f, clarify how many batches have been purified up to date and when do you plan to submit the updated endotoxin limits to the BLA. Your current endotoxin limits do not appear to be justified by your process

capability and could be lowered significantly. In addition, clarify why the endotoxin limit of the (b) (4) EU/mL) is higher than the limit of (b) (4) EU/mL).

### S.2.5 Process Validation and/or Evaluation

3.

4.

#### (Reference Sandoz, Inc. submissions on January 11 and January 29, 2016)

5. Response to information request submitted January 15, 2016. We acknowledge your response to Question 11 in the Information Request from the Agency dated December 11, 2015. You provided data showing the presence of the T7 peptide in the HIC post-E (b) (4) fraction peaks and, indirectly, the potency of the fractions. However, the Cys78-Cys88 disulfide bond (T7 peptide) is only one of four aberrant disulfide bonds that were identified in lots of GP2015 and US-licensed Enbrel. You did not provide data showing the impact of the other three aberrant disulfide bonds on potency or their levels relative to T7. In order to more fully understand the biological activity of the HIC post-peak, we recommend that you assess the post-peak fraction in the potency and binding assays.
6. Response to information request submitted January 29, 2016. We acknowledge your response to Question 13 in the Information Request from the Agency dated December 11, 2015. You provided preliminary data showing that the wrongly bridged disulfides in the post peak fraction can rearrange under specific conditions. Provide additional analytical data showing that biological activity has been restored. We refer you to a publication in

which the activity of the misfolded fraction is demonstrated for a different TNFR2-Fc fusion protein (Min K.H. and Lee G.M. Process Biochemistry 2015. 50: 1313-1317.)

7. Response to information request submitted January 15, 2016. We acknowledge your response to Question 15 in the Information Request from the Agency dated December 11, 2015. Your analysis of TNF- binding and apoptosis included 7 lots each of US-licensed Enbrel and EU-approved Enbrel lots that were beyond their expiration dates at the time of testing. Analytical testing of product lots should be performed prior to their expiration dates. Therefore, provide data for additional lots using US-licensed Enbrel and EU-approved Enbrel that are within their expiration dates.

**(Reference BLA 761042 3.2.R)**

8. In 3.2.R. "Comparability Drug Substance Phase III - Phase III Resupply", there are three wrongly bridged disulfide bonds shown in Figure 6-2, while in 3.2.R. "Biosimilarity with Reference Product", section 4.1.1.4 Figure 4-13 identified four wrongly bridged disulfide bonds. The disulfide bond not shown in Figure 6-2 is C18-C74. Please clarify which Figure is correct.

If you have any questions, please contact me at 301-796-0962 or [keith.olin@fda.hhs.gov](mailto:keith.olin@fda.hhs.gov).

Sincerely,

**Keith J. Olin -S**

Digitally signed by Keith J. Olin -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Keith J. Olin -S,  
0.9.2342.19200300.100.1.1=1300214407  
Date: 2016.02.26 13:29:28 -05'00'

CDR Keith Olin, Pharm.D.  
United States Public Health Service  
Senior Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** February 22, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Jessica Lee, PharmD <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 4

**Comments:** Please confirm receipt

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated, July 30, 2015, and Information Request dated, January 29, 2016. We have the following comments and request for information:

The Information Request dated, January 29, 2016, requested the following information from Study GP15-302:

- Dataset containing the listing of all ‘medications’ for psoriasis (if any) for each subject needed to compute the STRATA variable in the ADSL dataset. This information appears to be contained in the ‘external stratification file’ described in the define.xml file for the analysis datasets. Submit the information as an electronic dataset in .xpt format.

Prior therapy was a stratification factor in your study (no prior systemic therapy, any prior systemic therapy including biologic immunomodulating agents but no prior treatment with a TNF antagonist, or prior treatment with a TNF antagonist). As noted in your study report, the prior therapy classification used to stratify the randomization (STRATFPT) differs from the prior therapy variable used in the analysis (STRATA), as many subjects were reclassified following medical review. A dataset that identifies prior therapy information in a usable format is needed to independently verify the re-classifications made for the STRATA variable.

The dataset submitted on February 16, 2016 (oview2.xpt) does not include the prior therapy information. The concomitant medication (CM) dataset submitted in the original submission does include information on prior therapies; however, the CM dataset includes information for prior therapies for indications other than psoriasis, as well as concomitant medications taken during the study. It is a challenge to identify only the prior therapies for psoriasis as the dataset includes dozens of variations on the spelling of ‘psoriasis’ and no flags that might indicate which treatments were considered ‘prior therapies for psoriasis’ during the medical review. In addition, the dataset appears to have numerous duplicate observations that differ only in sequence number, but not for any other variable. A usable dataset that flags (or is limited to) the unique records of prior therapies for psoriasis (rather than all concomitant medications) that leads to the definition of the STRATA variable is still needed to continue our review. The dataset should include the following variables at a minimum:

- Variables with verbatim and standardized prior therapy name for each recorded prior therapy (similar to the variables CMTRT and CMDECOD in the CM dataset).
- Variable with following prior therapy categories: ‘Prior systemic psoriasis therapies’, ‘Biologic psoriasis therapies’, ‘Medical procedures and significant non drug therapies’, ‘TNF Antagonists’, ‘No prior systemic therapy’. These categories are listed as the categories used to define the STRATA variable in ADSL dataset in the ‘Comment’ column of the define.xml documentation for this variable.

Submit the above requested data as an electronic dataset in .xpt format.

Provide a response by Thursday, March 3, 2016. The information can be sent by email to Jessica Lee at [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov). Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Jessica Lee, Senior Regulatory Program Manager, at 301-796-3769.

Drafted by: KFritsch/MAlosh 2/19/16  
JLee 2/19/16

Initialed by: SBarnes 2/19/16  
TBBS 2/19/16  
KFritsch/MAlosh 2/22/16

Finalized by: JLee 2/22/16

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/s/

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JESSICA K LEE  
02/22/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

BLA 761042

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540

ATTENTION: Zhengyu Liu, Ph.D.  
Manager, US Biopharmaceutical Regulatory Affairs

Dear Dr. Liu:

Please refer to your Biologics License Application (BLA) dated and received on July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015.

We also refer to your correspondence, dated and received on November 25, 2015, requesting review of your proposed proprietary name, Erelzi and Erelzi Sensoready Pen.

We have completed our review of the proposed proprietary names, Erelzi and Erelzi Sensoready Pen, and have concluded that they are conditionally acceptable.

If any of the proposed product characteristics as stated in your November 25, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4845. For any other information regarding this application, contact Leila Hann, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
02/16/2016



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** January 29, 2016

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Jessica Lee, PharmD <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following request for information:

Submit the following information (or identify its location within materials already submitted) for Study GP15-302:

- Statistical program (or code fragment) used to define the STRATA variable in the ADSL dataset.
- Dataset containing the listing of all ‘medications’ for psoriasis (if any) for each subject needed to compute the STRATA variable in the ADSL dataset. This information appears to be contained in the ‘external stratification file’ described in the define.xml file for the analysis datasets. Submit the information as an electronic dataset in .xpt format.
- Some of the values of the DVTERM variable from the DV dataset have been truncated to 200 characters and their meaning is unclear. Provide the full (non-truncated) version of the following two comments:
  - i. *‘in eCRF patient did not take prior treatment with a TNF antagonist, however patient is not in strata "Any prior systemic therapy including biologic immunomodulating agents but no prior treatment with...’* (used for 36 subjects)
  - ii. *‘in eCRF patient took prior treatment with a TNF antagonist, however patient is in strata "Any prior systemic therapy including biologic immunomodulating agents but no prior treatment with a TNF...’* (used for 63 subjects)

Provide a response by Tuesday, February 9, 2016. The information can be sent by email to Jessica Lee at [Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov). Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Jessica Lee, Senior Regulatory Program Manager, at 301-796-3769.

Drafted by: KFritsch/MAlosh 1/28/16  
JLee 1/28/16

Initialed by: SBarnes 1/28/16  
TBBS 1/29/16  
KFritsch/MAlosh 1/29/16

Finalized by: JLee 1/29/16

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/s/  
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JESSICA K LEE  
01/29/2016



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** December 18, 2015

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Leila P. Hann <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 6

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following comments and request for response:

The following issues concern the PFS:

1. After review of your submission, it does not appear that you have performed any mechanical safety testing on the final assembled pre-filled syringe (PFS) with needle safety device (NSD) presentations. Conduct mechanical safety testing (i.e. resistance to component separation, drop testing, freedom from unacceptable damage to or loss of medication volume due to mechanical forces exerted by the system, resistance of system components to damage from shipping, etc.) after preconditioning and aging. Provide the test reports with protocol, acceptance criteria, rationale of acceptance criteria, and results of the tests.
2. Under 3.2.R, you reference design verification documents throughout the Technical Summary Needle Safety Device documents as support of the technical characteristics and performance of your device. The design verification information is critical to assessing the safety and efficacy of the combination product device.
  - a. Provide the following documents referenced in regard to the Technical Summary Needle Safety Device: GP2015\_PFS\_25\_50\_in (b) (4)\_DIR, GP2015\_PFS\_25\_50\_in (b) (4)\_DVERPL, GP2015\_PFS\_25\_50\_in (b) (4)\_DVERP1, GP2015\_PFS\_25\_50\_in (b) (4)\_DVERR1, GP2015\_PFS\_25\_50\_in (b) (4)\_DVERSR, and 8046 0017b
  - b. Include a rationale for all acceptance criteria within your design verification testing
3. The reviewer was unable to locate the performance testing (i.e. dose accuracy, injection depth, injection time, activation force, etc.) completed on the final finished combination product of the PFS with NSD. You note in your Technical Summary Needle Safety Device under 3.2.R that certain functional testing is completed prior to lot release of the PFS with NSD, however this functional testing is only related to the Needle Safety Device. Provide documentation demonstrating that the final finished combination product performs according to your design requirements and specifications in order to validate your device.
  - a. Identify all essential performance requirements for the PFS with NSD.
  - b. Provide performance testing data of the PFS with NSD after all preconditioning and aging activities up to the labeled date of expiry. Provide the test protocols and reports for these verification tests. Include a rationale for the acceptance criteria.
4. Within the Technical Summary Needle Safety Device, you state that the NSD has been cleared under 510(k) submissions K011369 and K060743, however upon review of these 510(k) submissions, it does not appear that the NSD was evaluated according to the “Guidance for industry and FDA Staff: Medical Devices with Sharps Injury Prevention

Features” issued in 2005. Note that for the review of a combination product, a 510(k) clearance of a device constituent part does not necessarily satisfy the level of safety and performance that the Agency expects. Therefore, provide documentation that the NSD you plan to commercially release is in compliance with the aforementioned Guidance and provide any test reports that prove compliance with the Guidance, if applicable.

5. You state that you have performed transportation validation activities for the PFS with NSD. Within Table 9-5 of your Technical Summary Needle Safety Device document, you reference transportation validation documents for the PFS with NSD; however, they are not included in your submission. Provide the transportation validation documents referenced in Table 9-5 to ensure that the PFS and NSD resists damage and maintains all essential performance requirements after transportation. For more information, refer to Designation: D4169 – 14, Standard Practice for Performance Testing of Shipping Containers and Systems.
6. You have provided shelf-life studies to verify the stability of the PFS with NSD; however, you reference a change in the assembly process of the NSD. In your Technical Summary Needle Safety Device you reference a risk assessment of the assembly process, claiming that the assembly process has no impact on the shelf life of the combination product. Provide the referenced risk assessment of the assembly process as support for the claim that the assembly process has no impact on the shelf life of the combination product.
7. You reference risk management documentation within the Technical Summary Needle Safety Device document, however these documents have not been provided within the submission. Please note that within risk management documentation, the Agency expects you to provide risk analysis information. Risk analysis information characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable misuse, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system. Provide the documents listed in Table 8-1, including GP2015\_PFS\_25\_50\_in (b)(4) RMUEP, (b)(4)-1mL-GP2015\_HID, (b)(4) HID\_SSI SD, and GP2015\_PFS\_25\_50\_in (b)(4) RA-API so that they may be reviewed for proper hazard identification and mitigation.
8. Describe the pre-filled syringe used in your clinical studies (GP15-101, GP15-102, GP15-104) and compare these devices to the to-be marketed pre-filled syringe combination product.
9. Describe the pre-filled syringe used in the GP15-103 study (syringe comparison to autoinjector) and compare to the syringe used in the GP15-101, GP15-102, and GP15-104 clinical studies.
10. The Agency is concerned that there is no clear indication or feedback to the user signaling that the entire dose has been expelled from the PFS with NSD device presentations. While the needle safety device activates upon release of the plunger, this does not ensure that the full dose has been expelled from the device. If the user is not aware whether or not the entire dose has been delivered, the user could unintentionally stop the injection prematurely,

leading to under delivery, or continue the injection for longer than necessary. Therefore, provide assurance that the device notifies the user in a reliable way that the entire expected dose has been expelled from the PFS.

11. The Agency is concerned that the activation of the needle safety device for the PFS with NSD device presentation could promote under delivery of the drug if unintentionally activated. The needle safety device is designed to activate once the user has pushed the plunger past a certain position on the needle safety device, however there is no design feature in place to ensure that the activation of the needle safety device can only activate after the entire dose has been delivered. Therefore, provide mitigation strategies you have in place for the risk of the needle safety device prematurely activating before the user can inject the entire expected dose.
12. You note in your summative AIN457 Human Factors study that a participant unintentionally forced the needle cap off of the PFS and began unintentionally released medication by pressing down on the plunger. The Agency is concerned that the force required to remove the needle cap of the PFS with NSD device presentations is low enough to allow for the user to unintentionally force the needle cap off and begin unintentionally expelling the drug product by pushing against the syringe plunger. Update your risk analysis accordingly and provide risk mitigation strategies you have in place to prevent an unintentional cap removal or a rationale for why the risk of unintentional cap removal is acceptable. Include the force required to remove the needle cap in your rationale.

#### Biocompatibility of the PFS:

13. The biocompatibility section within the 3.2.R Technical Summary Needle Safety Device states that Biocompatibility testing was performed for the NSD in compliance with ISO 10993-1 standard and all results met the respective requirements. Provide the test protocols and test reports for the cytotoxicity, intracutaneous reactivity, and sensitization testing performed on the NSD.
14. A biocompatibility evaluation should be performed on all patient contacting components for the final finished PFS with NSD device. Provide the biocompatibility testing for all patient contacting components including the pre-filled syringe. Additionally, provide a list of the materials within all patient contacting materials. This should include materials used in the manufacture and processing of the proposed device (i.e., plasticizers, additives, surfactants, colorants, adhesives). If you are relying on biocompatibility information from previously cleared or approved submissions, provide a letter of authorization for those submissions.

#### **The following issues are concerning the autoinjector:**

15. Under 3.2.R, you reference design verification documents throughout the Technical Summary (b)(4) Device documents as support of the technical characteristics and performance of your device. The design verification information is critical to assessing the safety and efficacy of the combination product device.

- a. Provide the following documents referenced in regard to the (b) (4) Auto-Injector in Table 9-1 of the Technical Summary (b) (4) Device document: 0154-010-IR-S002, (b) (4) GP2015\_50\_DVERPL, (b) (4) GP2015\_50\_DDPLAN, (b) (4) GP2015\_50\_PRDESC, GP2015\_50\_DEVEP\_Packaging, (b) (4) GP2015\_50\_DVERR\_Packaging, 0154-010-OT-0001, (b) (4) GP2015\_50\_HID\_02, (b) (4) GP2015\_50\_URS\_01
  - b. Include a rationale for all acceptance criteria within your design verification testing
16. 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. A listing of essential system level requirements for the autoinjector.
  - b. Information which verifies the essential system level requirements (see bullet 16a. above) using final finished batch release combination product.
17. You state that you have performed transportation validation activities for the auto-injector device presentations. Within Table 9-5 of your Technical Summary (b) (4) Device document, you reference transportation validation documents for the auto-injector; however, they are not included in your submission. Provide the transportation validation documents referenced in Table 9-5 to ensure that the device system components resist damage and maintain all essential performance requirements after transportation. For more information, refer to Designation: D4169 – 14, Standard Practice for Performance Testing of Shipping Containers and Systems.
18. In study GP15-103 you demonstrated PK similarity between administration of GP2015 with the auto-injector and the PFS, as well as safety and tolerance of a single dose in healthy males. However, it is unclear whether any device related failures were documented during this clinical study. Provide an analysis of any device related failures that were observed during the validation.

Provide a response by email (Jessica.Lee@fda.hhs.gov) or facsimile (301-796-9728), by 3pm, EST on Monday, December 28, 2015. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ December 15, 2015  
Cleared: S. Mollo/ December 17, 2015  
J. McMichael/ December 17, 2015  
TBBS/ December 17, 2015  
S. Barnes/ December 15, 2015  
Finalized: L. Hann/ December 18, 2015

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/s/  
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LEILA P HANN  
12/18/2015



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** December 15, 2015

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Leila P. Hann <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following comments and request for response:

As part of an assessment of safety and immunogenicity, study GP15-302 includes a single transition such that a subset of patients initially randomized to EU-approved Enbrel will be re-randomized at Week 12 to either continue on EU-approved Enbrel or undergo a single transition to GP2015. A similar re-randomization occurs at Week 12 for patients initially randomized to GP2015. Consequently, the study Treatment Period 2 has 4 treatment arms: (1) continuous EU-approved Enbrel, (2) single transition from EU-approved Enbrel to GP2015, (3) continuous GP2015, and (4) single transition from GP2015 to EU-approved Enbrel. However, the 120 Day Safety Update, submitted on 24 November 2015, presents the safety data for study Treatment Period 2 bypooled continued (i.e. pooled groups 1 and 3) vs. pooled switched (i.e. pooled groups 2 and 4) treatments. By presenting the data this way, a descriptive comparison of safety and immunogenicity between patients who continued EU-approved Enbrel (group 1) vs. those who undergo a single transition from EU-approved Enbrel to GP2015 (group 2), is not possible. Submit the safety and immunogenicity data for study Treatment Period 2, Weeks 12-30, by actual treatment arm rather than by pooled treatment groups.

Provide a response by email ([Jessica.Lee@fda.hhs.gov](mailto:Jessica.Lee@fda.hhs.gov)) or facsimile (301-796-9728), by 3pm, EST on Friday, January 04, 2015. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ December 14, 2015  
Cleared: R. Glaser/ December 14, 2015  
N. Nikolov/ December 14, 2015  
TBBS/ December 14, 2015  
S. Barnes/ December 14, 2015  
Finalized: L. Hann/ December 15, 2015

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/s/  
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LEILA P HANN  
12/15/2015



BLA 761042

## INFORMATION REQUEST

Sandoz, Inc.  
Attention: Zhengyu Liu, Ph.D.  
Manager, U.S. Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your original Biologics License Application received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept).

We are reviewing your submission and have the following comments related to Immunogenicity, Microbiological Quality of the Drug Product, Drug Substance Impurities and your response to the November 20, 2015 Information Request Question 2, submitted December 11, 2015. We request a prompt written response in order to continue our evaluation. Please submit your response prior to January 15, 2016. If the data are not currently available, provide an estimate of when the data are likely to be submitted to the FDA.

### **Immunogenicity: Questions 1 - 5**

**Validation of the electrochemoluminescence (ECL) assay to detect binding anti-drug antibodies (ADAs) and the enzyme-linked immunosorbent assay (ELISA)-based competitive ligand-binding (CLB) assay to determine the neutralization activity of the confirmed positive ADAs.**

1) Requests concerning the determination of assay cut-points:

- a. The screening, confirmatory, and neutralization activity assay cut-points were determined using commercial sera from psoriasis patients purchased from Sera Laboratories International. However, the confirmation of the cut-points using serum samples from pre-dosed GP15-302 patients was not provided. In order to evaluate the suitability of the cut-points determined during assay validation for Study GP15-302, provide the screening, confirmatory, and neutralization assay cut-points using pre-dosed in-study patient samples.

- b. Both ECL and CLB assays evaluated psoriasis patient serum samples for the presence of outliers during cut-point determination; however, sufficient statistical analysis for outliers was not provided in the validation reports (BA13019-R and BA14023-R, respectively) and the analytical report (BA14001-R). Provide a statistical analysis to support the determination of outliers present or absent in the distribution data.
- c. Sufficient statistical analysis was not provided to support the determination of the ECL confirmatory cut-point (BA13019-R). Provide the statistical analysis used to justify a fixed cut-point; the means and variances of assay signal from the different runs should be compared by a mixed effects model and Levene's test, respectively, to determine the suitability of a fixed or floating cut-point.
- d. While two analysts ran the cut-point determination experiments from 30 individual psoriasis patient serum samples during CLB assay validation (BA14023-R), only analyst (b)(4) was used to determine the cut-point. Data from both analysts should be used to determine the CLB cut-point. Provide the data and statistical analysis from both analysts for the cut-point determination. Additionally, percent signal inhibition values for each sample run should be provided for both analysts.
- e. The use of a fixed cut-point and a parametric method in determining the cut-point value for the CLB assay was not justified by supportive data generated during validation (BA14023-R). The means and variances of assay signal from the different runs should be compared by a mixed effects model and Levene's test, respectively, to determine the suitability of using a fixed or floating cut-point. Provide the statistical analysis of data used to support the fixed cut-point.
- f. Regarding the method used to determine the CLB assay cut-point (BA14023-R) and the re-determined ECL screening cut-point (BA14001-R), we note that Shapiro-Wilk analysis of the transformed data did not prove data normality and the central limit theorem was used to anticipate data normality to support the use of a parametric approach. This is not acceptable. You should determine the skewness of the data, and if outliers are suspected but not verified by statistics, you should consider using a robust parametric approach for cut-point determination as outlined in the following reference:

Shankar G, Devanarayan V, Amaravadi L, Barrett YC, Bowsher R, Finco-Kent D, Fiscella M, Gorovitis B, Kirschner S, Moxness M, Parish T, Quarmby V, Smith H, Smith W, Zuckerman L, Koren E. 2008. Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. *J Pharm. Biomed. Anal.* 48(5): 1267-81.

2) Requests regarding the drug tolerance evaluation of the ECL and CLB assays:

- a. Drug concentrations of GP2015 below trough levels (4-10 µg/ml) prevented the detection of low levels of binding ADAs (200 ng/ml) during the analysis of drug tolerance for the ECL assay (BA13019-R). This suggests that drug interference is occurring at the assay sensitivity (116.5 ng/ml) and low positive control (LPC, 158.3 ng/ml) levels. Although drug tolerance up to 50 µg/ml is demonstrated for detection of ADAs at 600 ng/ml, this concentration of ADAs is above the recommended range of assay sensitivity for screening assays (200-500 ng/ml). Provide all available data to support the drug tolerance of the ECL assay to detect ADAs within the sensitivity range of 200 ng/ml to 500 ng/ml.
- b. The drug tolerance for the CLB assay, validated for psoriasis patients (BA14023-R), is below the trough levels of GP2015 (< 4-10 µg/ml) for detection of neutralizing ADAs at 1,500 ng/ml (polyclonal positive control antibody), suggesting that drug interference is occurring at the assay sensitivity (935.4 ng/ml) and LPC (1,852.7 ng/ml) levels. The data suggest that the assay can detect neutralizing activity if the ADAs are at a concentration of 7,500 ng/ml, which represents a poor tolerance to on-board drug. Provide all available data supporting a justification for the suitability of the CLB assay to detect neutralizing activity.

3) Requests concerning the matrices used in the ECL and CLB assays:

- a. An evaluation of interference by serum components, such as hemoglobin and lipids, and the derivation of the minimum required dilution of 1:3 were not provided in the assay validation reports (BA13019-R and BA14023-R, respectively). Provide all available data on the possible interference of serum components from psoriasis patients on the ability of the ECL assay and the CLB assay to detect binding and neutralizing ADAs, respectively.
- b. The validation reports for the ECL and CLB assays (BA13019-R and BA14023-R, respectively) did not describe whether individual serum samples were pre-screened for pre-existing antibodies and statistically evaluated for the presence of outliers prior to the pooling of serum samples from healthy volunteers or psoriasis patients. Inclusion of outliers in the serum pools can lead to greater variability and/or higher background. Provide data and a statistical analysis to indicate that the samples comprised of the pooled groups do not contain pre-existing antibodies.

4) The CLB assay used both a polyclonal positive control antibody (BioGenes GmbH) and a monoclonal positive control antibody (LifeSpan BioScience, Inc.) during the validation for testing of psoriasis patient serum. Sufficient information and data regarding the monoclonal positive control antibody were not provided in the validation report (BA14023-R) to

determine the suitability of using the monoclonal positive control antibody during assay validation. Provide the following detailed information regarding:

- a. The preparation and storage of diluted psoriasis patient serum samples spiked with the monoclonal positive control antibody. If pre-dilution samples were also made with the monoclonal antibody, and stored, sufficient stability data should be provided.
  - b. The values for assay sensitivity and a low positive control specific to the monoclonal positive control antibody. Data and a statistical analysis should also be provided to support the values.
  - c. Intra- and inter-precision analysis of the monoclonal positive control antibody at low, mid, and high concentrations spiked in the diluted (1:3) psoriasis serum pool.
  - d. Specificity analysis to demonstrate that the detection of neutralizing ADAs, using both polyclonal and monoclonal positive control antibody preparations, over a broad range of concentrations can be specifically and similarly depleted with increasing concentrations of EU-approved Enbrel and GP2015.
- 5) GP2015 was used at a concentration of 20 ng/ml in the CLB assay. However, data to support the suitability of the GP2015 concentration of 20 ng/ml were not provided in the validation report (BA14023-R). Provide an activity-response curve to demonstrate that 20 ng/ml of GP2015 is within the linear range of the activity-curve.

### **Drug Product Quality Microbiology: Questions 6 - 10**

#### 6) P.2 Pharmaceutical Development

- a) Provide study reports for bacterial retention studies and integrity test (bubble point and forward flow) validation studies for the sterilizing filters.
- b) Submit the Rabbit Pyrogen Test report to the 351(k) BLA.
- c) The application states that filter integrity testing is [REDACTED] (b) (4) [REDACTED] using either the forward flow or bubble point tests. Indicate the factors that are used to determine which test is used. Indicate if this testing is done for both the bioburden reduction and sterilizing filters.

#### 7) P.3.3 Description of Manufacturing Process and Process Controls

- a) Indicate if the formulation buffer is monitored for bioburden and endotoxin prior to formulation. Indicate the established limits for the buffer solution. Also, indicate if the buffers are filtered prior to use.

b) Confirm that bioburden samples are collected [REDACTED] (b) (4) sample points.

8) P.3.4 Control of Critical Steps and Intermediates

a) Specify the sample and test volumes used in the [REDACTED] (b) (4) bioburden testing.

b) Please clarify why the bioburden action limits are [REDACTED] (b) (4) CFU/[REDACTED] (b) (4) mL for Gram negative bacteria and [REDACTED] (b) (4) CFU/[REDACTED] (b) (4) mL for total microbial count for bioburden samples taken at [REDACTED] (b) (4).

c) Currently, endotoxin testing is performed [REDACTED] (b) (4). Endotoxin should be monitored throughout the process along with bioburden to ensure a non-pyrogenic product. Please implement in-process endotoxin testing and indicate proposed endotoxin limits for in-process pools.

9) P.3.5 Process Validation and/or Evaluation

a) The [REDACTED] (b) (4) of NMT [REDACTED] (b) (4) hours was established based on growth promotion studies. However, the duration of the validation studies was only 8 hours and 24 minutes. Clarify if additional studies were conducted and submit them to the 351(k) BLA; otherwise, limit the maximum hold time [REDACTED] (b) (4) to [REDACTED] (b) (4) hours.

b) Provide the number of rejected vials from each media fill run on [REDACTED] (b) (4)

c) Provide data from the most recent requalification of the [REDACTED] (b) (4) relevant for GP2015 PFS.

d) With regard to [REDACTED] (b) (4) qualification studies, provide a description and/or diagram of the locations of the [REDACTED] (b) (4).

e) Provide and update on the progress of the transport validation studies currently in progress and indicate when the final report will be submitted to the 351(k) BLA.

10) P.5 Control of Drug Product

a) Both the rapid sterility test and compendial test have been validated to test the sterility of GP2015. Specify when the rapid sterility test would be used as opposed to the compendial test.

b) Provide descriptions of the [REDACTED] (b) (4) bioburden test, compendial sterility test, and bacterial endotoxins (LAL) test.

### **Drug Substance Impurities Questions 11-14**

11) 3.2.S.3.2 Impurities 6.9.4 Classification – product related variants

Reference is made to the post peak fractions of GP2015 that can be separated from the main active peak by reverse phase chromatography (RPC) and consist mainly of inactive wrongly disulfide variants. Provide data showing the potency and TNF binding activity associated with this fraction compared with the main peak and unseparated product for both GP2015 and US-licensed Enbrel. You should assess the level of purity of each isolated peak for interpreting the results.

12) 3.2.S.3.2 Impurities 7.4.1 Qualitative characterization of RPC peaks

Figure 7-25 shows an SDS PAGE gel comparing the GP2015 DS and DP main and post RPC peaks with the US-licensed Enbrel main and post peak. The US-licensed Enbrel post peak is reduced while the remaining samples are all non-reduced. Provide a rationale for not including the non-reduced US-licensed Enbrel in the analysis.

13) We recommend that you perform studies on both GP2015 and US-licensed Enbrel to assess if the wrongly bridged disulfide bonds are reversible in human serum. We recommend a time course experiment at 37°C to establish if the wrongly bridged disulfide bonds are modified in the presence of oxidoreductases present in serum and could convert to the active form found in the RPC main peak.

14) To more fully support the totality of the evidence, we suggest that you explore the relationship between the presence of the wrongly bridged disulfide variant and the PK bioanalytical method and PK similarity data. In comment 11, we recommend that you isolate the main active peak and the post peak by RPC to assess their potency.

- a. Provide a response regarding your ability to assess the binding of the isolated peaks by the capture and detection reagents used in the bioanalytical assay. If possible, we recommend that you perform this study with both sets of reagents that were used for studies GP15-101/GP15-102 and GP15-104. We also recommend, if feasible, to assess any differences in affinity of these reagents for the active peak and the RPC-post peak.
- b. If you have sample retains from the PK studies, we suggest that you assess the samples for active versus wrongly bridged disulfide bond molecules. It may be feasible to accomplish this by isolating GP2015 and US-licensed Enbrel or EU-approved Enbrel from patient samples and assessing the enriched samples using the method to quantitate the wrongly bridged T7 peptide.

**December 11, 2015 Response to Information Request Question 2 Question 15**

15) Regarding the TNF $\alpha$  binding assay, we acknowledge that you will provide data for at least 3 additional batches of US-licensed Enbrel in January 2016. However, we do not agree with your assertion that [REDACTED] (b) (4). In order to more fully support the totality of the evidence and to meet the established criteria for equivalence testing, you should submit data from a minimum of 10 lots, which can include the three lots submitted in the original BLA (See November 20, 2015 IR Question #3). In addition, for both the TNF $\alpha$  binding and TNF $\alpha$  neutralization assays, you should also provide data for a minimum of 10 lots of EU-Enbrel to support the analytical bridge.

If you have any questions, please contact me at 301-796-0962 or [keith.olin@fda.hhs.gov](mailto:keith.olin@fda.hhs.gov).

Sincerely,

**Keith J. Olin -S**

Digitally signed by Keith J. Olin -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, cn=Keith J. Olin -S,  
0.9.2342.19200300.100.1.1=1300214407  
Date: 2015.12.11 14:34:14 -05'00'

CDR Keith Olin, Pharm.D.  
United States Public Health Service  
Senior Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** December 02, 2015

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Leila P. Hann <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated July 30, 2015. We have the following comments and request for response:

We note that the bioanalytical methods to quantify etanercept in serum samples from healthy volunteers in different clinical studies used different versions of the same SOP (SOP PV05102, version 02 for clinical studies GP15-101 and GP15-102; SOP PV05102, version 03 for clinical studies GP15-103 and GP15-104). Clarify if each version of the method captures both active Enbrel/GP2015 and their wrongly bridged variants.

Provide a response by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by 3pm, EST on Friday, December 04, 2015. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ November 23, 2015  
Cleared: M. Shapiro/ November 23, 2015  
P. Ji/ November 23, 2015  
Y. Ren/ November 23, 2015  
TBBS/ December 01, 2015  
S. Barnes/ November 24, 2015  
Finalized: L. Hann/ December 02, 2015

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LEILA P HANN  
12/02/2015



BLA 761042

## INFORMATION REQUEST

Sandoz, Inc.  
Attention: Zhengyu Liu, Ph.D.  
Manager, U.S. Biopharmaceutical Regulatory Affairs  
100 College Road West  
Princeton, NJ 08540

Dear Dr. Liu:

Please refer to your original Biologics License Application received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015, a proposed biosimilar to US-licensed Enbrel (etanercept).

We are reviewing your submission and have the following comments. We request a prompt written response in order to continue our evaluation. Please submit your response prior to December 11, 2015. If the data are not currently available, provide an estimate of when the data are likely to be submitted to the FDA.

**Items 1-10 pertain to the analytical similarity studies. We are requesting additional analytical data to support a demonstration that GP2015 is highly similar to US-licensed Enbrel and the analytical bridge between GP2015 US-licensed Enbrel, and EU-approved Enbrel.**

- 1) 3.2 R CQA Assessment, Section 2.3, describes the calculation of criticality scores for variants and impurities. In general, we agree with the criticality (very high, high, moderate, low, or very low) assignments for each quality attribute shown in Table 3-1. However, you should provide an explanation for the values assigned in the equation in Figure 2-1 and what they represent.
- 2) We have the following comments regarding your statistical approach to support a demonstration that the products are highly similar:
  - a. TNF-alpha neutralization and TNF binding should be analyzed using the equivalence method. For TNF binding, you provided data for 8 GP2015 drug product lots, but only three lots of US-licensed Enbrel. Provide an updated analysis using additional lots of US-licensed Enbrel.
  - b. For TNF-alpha neutralization using the Reporter Gene Assay (RGA), you provided data for 8 GP2015 drug product lots and 25 lots of US-licensed Enbrel. This is a sufficient number of US-licensed Enbrel lots; however, we note that most of the US-

licensed Enbrel lots have lower potency relative to the GP2015 lots. We also note that most of the US-licensed Enbrel lots with lower potency have expiration dates ranging from 2014 through 2015, suggesting that many may have been manufactured (b) (4). If available, provide data from additional US-licensed Enbrel lots that were more likely to have been manufactured during (b) (4).

- c. We do not agree with your approach to Tier 2 analysis. Please provide the analyses using Quality Range (mean  $\pm$  X SD) instead of Tolerance Intervals, and justify the value of the SD used for each analysis.
  - d. Regarding the assignment of quality attributes to different tiers for evaluation of the attributes, we do not intend that all attributes ranked as very high or high criticality be assigned and tested using Tier 1 methods. We intend for Tier 1 analysis to be applied, in general, to attributes of very high or high criticality that are related to a product's mechanism of action, which are amenable to equivalence testing. Other quality attributes determined to have very high or high criticality could be assigned to Tier 2 or Tier 3 analysis if appropriately justified.
- 3) We currently recommend that you use a statistical approach to evaluate quality attributes of proposed biosimilar products that is consistent with the risk assessment principles set forth in the International Conference on Harmonization Quality Guidelines Q8, Q9, Q10, and Q11. Consistent with the principles set forth in these guidances, your program should implement an analytical similarity assessment that is based on a tiered system in which approaches of varying statistical rigor are used. One approach to determining the tier to which a particular quality attribute would be assigned would depend upon a criticality risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and immunogenicity with quality attributes being assigned to tiers commensurate with their risk.

For your program, equivalency testing would be recommended for quality attributes with the highest risk ranking (Tier 1) and generally would include assay(s) that evaluate clinically relevant mechanism(s) of action of the product for each indication for which approval is sought. We recommend that you consider the use of quality ranges (mean  $\pm$  X  $\sigma$ , where X should be appropriately justified) for assessing quality attributes with lower risk ranking (Tier 2), and an approach that uses raw data/graphical comparisons for quality attributes with the lowest risk ranking (Tier 3).

In addition to criticality, other factors should be considered in assigning quality attributes and assays to a particular tier using this approach. This approach includes, but it is not limited to, the levels of the attribute in both the reference product and proposed biosimilar product (as determined by your testing), the sensitivity of an assay to detect differences between products, if any, and an understanding of the limitations in the type of statistical analysis that can be performed due to the nature of a quality attribute.

FDA also recommends that you carefully assess your analytical similarity plan to identify and address any other factors that could potentially impact the ability to demonstrate that GP2015 is highly similar to the reference product. This could include, for example, considering the ages of the GP2015 and reference product lots tested, optimizing assays and

pre-specifying the criteria under which wider similarity acceptance criteria for a particular assay would be considered appropriate.

We think it would be appropriate for you to consider a statistical approach, such as the one set forth below based on FDA's current thinking on the topic, to evaluate certain quality attributes of the proposed biosimilar and the reference product. You may propose alternative statistical approach(es) to evaluate quality attributes and support a demonstration that GP2015 is highly similar to US-licensed Enbrel.

Further, we note that while a statistical approach to evaluate quality attributes of a proposed biosimilar product may be considered in support of a demonstration that the proposed biosimilar product is highly similar to the reference product, FDA's determination that a proposed biosimilar product is highly similar to the reference product will be based upon the totality of the evidence relevant to the assessment.

A potential approach for the different statistical tiers is described below:

- a. **Tier 1 (Equivalence Test):** One needs to test against the following null hypothesis.

$H_0 : \mu_B - \mu_R \leq -\delta \quad \text{or} \quad \mu_B - \mu_R \geq \delta \geq \delta$  where  $\mu_B$  and  $\mu_R$  are the mean responses of the proposed biosimilar and reference product lots, respectively, and  $\delta > 0$  is the equivalence margin.

Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if the  $(1-2\alpha)100\%$  two-sided confidence interval of the mean difference is within  $(-\delta, \delta)$ . In this context, the equivalence margin,  $\delta$ , would be a function of the variability of the reference product as identified in studies by the biosimilar applicant ( $\sigma_R$ ).

- b. **Tier 2 (Quality Range Approach):** The quality range of the reference product for a specific quality attribute is defined as  $(\hat{\mu}_R - X \hat{\sigma}_R, \hat{\mu}_R + X \hat{\sigma}_R)$  where the standard deviation multiplier (X) should be appropriately justified.

Acceptance Criterion: Analytical similarity would be accepted for the quality attribute if a sufficient percentage of test lot values (e.g. 90 percent) fall within the quality range.

- c. Please note that each lot contributes one value for each attribute being assessed. Thus,  $\sigma_R$  refers to the standard deviation of those lot values of the reference product.
- d. Ideally, the reference variability,  $\sigma_R$ , should be estimated from testing different lots than those used in statistical equivalence test. This may be a challenge when there are a limited number of lots. The sponsor should provide a plan for how the reference variability,  $\sigma_R$ , will be estimated with a justification for the approach and identify the lots that will be used.
- e. We would also recommend that the same number of replicates be performed within each proposed biosimilar lot as within each reference product lot, and that the same lots be used for equivalence testing, quality range testing, and visual assessment of graphical displays.

- f. Please note that high assay variability would not be a justification for a large  $\sigma_R$ . In such a situation, the assay would need to be optimized and/or the number of replicates increased to reduce variability.
- g. In cases where the equivalence margins or quality ranges are too wide, it may be scientifically justified and appropriate to narrow the margins or range.

One potential statistical approach to evaluate quality attributes is based on a standard statistical test of equivalence with the margin defined as a function of the reference product variability (e.g.,  $c \times \sigma_R$ ). The constant  $c$  would be selected as the value that provides adequate power to show equivalence if there is only a small difference in the true mean between the biosimilar and the reference product, when a moderate number of reference product and biosimilar lots are available for testing. If, for example, we selected  $\delta = 1.5 \sigma_R$  for all sample sizes used in equivalence testing to illustrate this potential statistical approach, the test would yield a positive result if the 90% confidence interval about the difference in sample means lies within  $(-1.5 \sigma_R, 1.5 \sigma_R)$ . If 10 biosimilar and 10 reference product lots, this test would have approximately 87% power when the true underlying mean difference between the proposed biosimilar and reference product lots was equal to  $\sigma_R / 8$ , assuming a test with  $\alpha = 0.05$ .

Note that with this potential approach, the margin would be a function of the reference product variability as demonstrated in testing by the biosimilar applicant; therefore, a larger margin would be used for attributes with larger variability. In addition, the confidence level would depend on the number of lots available for testing. For the more limited number of lots described in your briefing package, you may consider calculating the confidence interval with a lower confidence level to ensure adequate power. In this situation, the lower confidence level would be expected to be appropriately addressed by the final manufacturing control strategy. In contrast, when a moderate or greater number of lots are available for testing, the equivalence test would be based on a 90% confidence interval.

- 4) As stated in the Guidance for Industry ‘Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product (2015)’ under certain circumstances, a sponsor may use a non-U.S.-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the U.S.-licensed reference product. However, as a scientific matter, analytical studies and at least one clinical pharmacokinetic (PK) study and, if appropriate, at least one pharmacodynamics (PD) study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the U.S.-licensed reference product unless it can be scientifically justified that such a study is not needed. If a sponsor seeks to use data from an animal study or a clinical study comparing its proposed biosimilar product to a non-U.S.-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the U.S.-licensed reference product.

As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., the proposed biosimilar product, the U.S.-licensed reference product, and the non-U.S.-licensed comparator product), and is likely to also include bridging clinical PK and/or PD study data for all three products. All three pairwise comparisons should meet the pre-specified acceptance criteria for analytical and PK and/or PD similarity. The acceptability of such approach will be evaluated on a case-by-case basis, and should be discussed in advance with the Agency. For certain complex biological products, a modified approach may be needed.

We note that your statistical analysis of the three-way comparison is restricted to bioactivity, TNF- $\alpha$  binding, and content. Data from this limited number of analytical attributes is not sufficient to establish a robust 3-way analytical bridge (i.e., pair-wise comparisons of GP-2015, US-licensed Enbrel, and EU-approved Enbrel) necessary to justify the relevance of data obtained using EU-approved Enbrel to support a demonstration of biosimilarity to US-licensed Enbrel. The 3-way analytical bridge should include testing of all the quality attributes assessed in the analytical similarity exercise, which are ranked and subsequently analyzed using FDA's recommended statistical approach.

**Comments 5-10 are specific for certain methods described in 3.2.R "Biosimilarity with Reference Product"**

- 5) Section 4.1.1.7 describes amino acid analysis studies. An experimentally determined extinction coefficient was calculated using data from amino acid analysis of a single lot each of US-licensed Enbrel and GP2015. Provide a justification for the experimental method used to determine the extinction coefficient, and the approach that was used for calculating the experimental extinction coefficient.
- 6) Section 4.1.11 describes protein content of GP2015, which was determined using an extinction coefficient based on the declared content of batches of EU-approved Enbrel, US-licensed Enbrel and GP2015. The extinction coefficient should be experimentally determined using an analytical approach that is independent of the label claims of the originator. (see Q+A #I.12 in Guidance for Industry "Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009" (April 2015), available at <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm444661.pdf>).
- 7) Section 4.2.2 describes Additional Cell Based Assays (ADCC and CDC)
  - a. The analytical data show that GP2015 has lower ADCC activity compared to US-licensed Enbrel. You contend that ADCC is not part of the mechanism of action (MOA) for US-licensed Enbrel. Your method utilizes an immortalized NK cell line expressing Fc $\gamma$ RIIIa and an engineered HEK293 cell line that overexpresses membrane bound TNF $\alpha$ . A comparison of ADCC activity which uses PBMCs may represent a more relevant model to support this claim. In addition, you can provide

- further justification that ADCC is not a MOA for US-licensed Enbrel by citing relevant literature. See comment 8a related to non-fucosylated glycan structures.
- b. Section 4.2.2, Figure 4-117 shows the ADCC activity with different levels of mTNF on HEK cells. Submit experimental data, such as FACS analysis, that compare mTNF- $\alpha$  expression levels on LPS stimulated U937 cells and HEK293 cells transfected with mTNF. This type of analysis will provide more direct evidence that the observed trends in figure 4-117 are due to differences in TNF expression.
  - c. Section 4.2.2, Figure 4-118 shows that GP2015 is more effective at inducing a CDC response compared to US-licensed Enbrel. This result is not consistent with the results of the C1q binding assay, which show similar binding between GP2015 drug product lots and US-licensed Enbrel lots, while GP2015 drug substance lots have higher C1q binding than US-licensed Enbrel. Although the scientific literature suggests that etanercept binds poorly to C1q, it can induce low levels of CDC activity (Arora et al. 2009. Cytokine 45:124). Submit figures of the actual curves showing the CDC results over a range of concentrations and calculate the EC50. We recommend that you compare GP2015 and US-licensed Enbrel to an anti-TNF mAb, which were shown in Arora et al. to have much higher C1q binding and CDC activity. Additional justifications for these differences and the mechanism(s) responsible for the elevated CDC may need to be identified and controlled.
  - d. Section 4.2.1. Data were presented in Table 4-57 that include apoptosis (TNF- $\alpha$  neutralization), but these data were not evaluated in the same way that was performed for the TNF-alpha and TNF-beta RGAs (Figures 4-108 and 4-109). We note that the trends for the apoptosis assay (higher potency for US-licensed Enbrel) contradict those observed in the TNF-alpha RGA (lower potency for US-licensed Enbrel). Provide an explanation for why the trends in the data are different.
- 8) Section 4.1.5 describes the assessment of glycosylation:
- a. Section 4.1.5.2. The evaluation of non-fucosylated N-glycans did not include an assessment that was limited to the Fc region. In addition, the calculation of the non-fucosylated N-glycans does not include non-fucosylated glycans such as Man5. Differences in non-fucosylated N-glycans on the Fc-region of GP2015, US-licensed Enbrel, and EU-approved Enbrel could explain the differences in ADCC activity. Provide data separating the N-glycan structures of the Fc-region from the TNF receptor region of GP2015.
  - b. Table 4-27 includes a column “mol sialic acids/6 mol N-glycans”. Provide an explanation regarding the “6 mol N glycans.” Provide a rationale for including these data.
- 9) Section 4.1.7.6, Heterogeneity Size: FFF-MALLS. We believe there is a typographical error in Table 4-36, where the units of measurement are given as [Da] instead of kDa. Update the 351(k) BLA to include a correct table.
- 10) Section 6.3.2.5, Forced Degradation Light Exposure: Table 6-35 “TNF-alpha RGA after light exposure” includes data from a lot labelled (b)(4) (1029710), which does not appear in the listing of lots in Table 6-6 “GP2015 and Enbrel batches used for forced degradation study”.

A number of the figures also include data from this lot (e.g. Figures 6-20 and 6-22). Clarify if data from this lot is to be included in the submission and the country of origin of the lot.

**Questions 11 through 18 refer to Microbial Quality – Drug Substance (DS)**

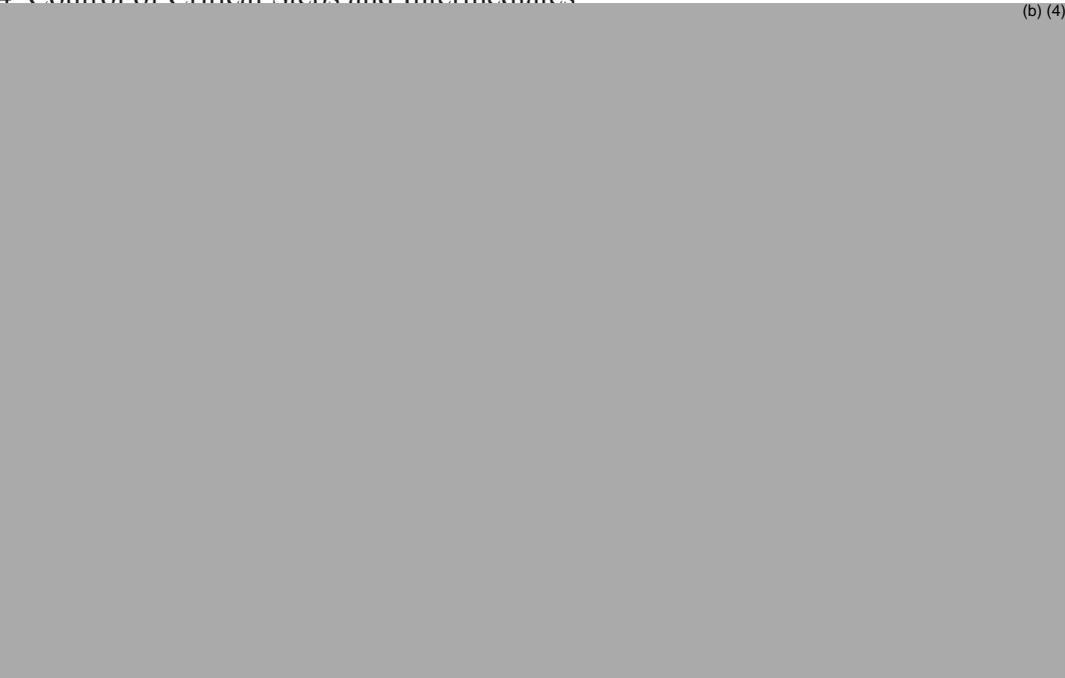
11) Section 2.2, Description of the Manufacturing Process and Process Controls

- a.
- b.
- c.
- d.
- e.



12) Section 2.4 Control of Critical Steps and Intermediates

- a.
- b.
- c.
- d.
- e.
- f.
- g.



13) Section 2.5, Process Validation and/or Evaluation – Process Performance Qualification (PPQ) Batches:

- a. Clarify to which steps correspond IN0, IN1, IN2, IN3, and IN4 shown in Tables 3-9 and 3-14.
- b. Tables 3-35 and 3-53 show the DS endotoxin acceptance limit to be  $\leq$  [redacted] (b) (4) and is inconsistent with the acceptance limit of  $\leq$  [redacted] (b) (4) from section 2.3.S.4; clarify which is the correct endotoxin specification for DS and amend the BLA to include the correct units.

- c. Release data for the Process Validation Batches (PVB) in manufacturing (b) (4). Table 3-53 shows PVB B213820, B213822, and B213823, which correspond to the PVB manufactured (b) (4). Clarify and amend the BLA if the information is incorrect.

14) Section 2.5, Process Validation and/or Evaluation – Validation of maximum in-process hold times:

The hold time study conducted in the Process Validation Batches does not support microbial control during the maximum hold time because the hold times were lower than the maximum hold times. If you plan to support the maximum (b) (4) hold times (b) (4) describe how the study was conducted, i.e., (b) (4) and correlate those conditions to routine manufacturing conditions to support worst case. Indicate if (b) (4) are covered in the study; if a (b) (4) approach was used, define the characteristics that constitute (b) (4). Indicate the number of runs that was conducted for (b) (4).

15) Section 2.5, Process Validation and/or Evaluation – (b) (4) studies:  
Include bioburden and endotoxin as part of the (b) (4) studies at scale. Samples should be taken after (b) (4).

16) Section 2.5, Process Validation and/or Evaluation – Shipping validation:

Provide a diagram showing the location of thermocouples in the maximum and 50% shipping loads and include location of thermocouples during routine shipping. Clarify if the shipping containers are transported in refrigerated trucks.

17) Section 4.2, Analytical Procedures:

Provide a detailed description of the bioburden and endotoxin methods for in-process and release samples.

18) Section 4.3, Validation of Analytical Procedures:

- a. For validation of the Endotoxins LAL method, the maximum valid dilution (MVD) for DS was calculated using an outdated endotoxin limit of (b) (4) EU/mg; amend the BLA to provide the current DS MVD.
- b. As indicated in question 12e, endotoxin limits for the (b) (4) are too high and should be tightened; MVD should be tightened accordingly.
- c. The endotoxin method qualification shows that the lowest dilutions used for all in-process and release samples are within specifications and results are not significantly different from the next qualified dilution. Higher dilutions result in lower endotoxin detection sensitivity. Justify using routine dilutions higher than the lowest qualify dilutions.

If you have any questions, please contact me at 301-796-0962.

Sincerely,

**Keith J. Olin -S**

Digitally signed by Keith J. Olin -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, cn=Keith J. Olin -S,  
0.9.2342.19200300.100.1.1=1300214407  
Date: 2015.11.19 15:08:34 -05'00'

CDR Keith Olin, Pharm.D.  
United States Public Health Service  
Senior Project Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE: November 10, 2015**

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Leila P. Hann <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original 351(k) BLA submission dated July 30, 2015, the Agency's information request September 17, 2015, and your response. We have the following comments and request for response:

In response to your proposed PLLR labeling changes following our recent information request dated September 17, 2015, we found that you did not provide a review and summary of the available information to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until this information request is fulfilled. No partial PLLR conversions may be made.

Submit the following by November 24, 2015:

- a review and summary of the available published literature regarding etanercept use in pregnant and lactating women,
- a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR and includes the required background risk statement and animal data risk statement in subsection 8.1 Pregnancy.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Provide an updated label by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by 5pm, EST on Monday, November 24, 2015. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ November 09, 2015  
Cleared: N. Nikolov/ November 09, 2015  
E. Radden/ November 09, 2015  
TBBS/ November 10, 2015  
S. Barnes/ November 09, 2015  
Finalized: L. Hann/ November 10, 2015

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/s/  
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LEILA P HANN  
11/10/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Silver Spring, MD 20993

BLA 761042

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Sandoz, Inc.  
100 College Road West  
Princeton, NJ 08540

ATTENTION: Zhengyu Liu, Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Liu:

Please refer to your Biologics License Application (BLA) dated and received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015.

We also refer to your correspondence, dated and received July 30, 2015, requesting review of your proposed proprietary name, (b) (4) and (b) (4) Sensoready.

We have completed our review of these proposed proprietary names and have concluded that these names are unacceptable for the following reasons:

The root name, (b) (4) is orthographically and phonetically similar to the currently marketed product (b) (4)

(b) (4)

(b) (4)

We also note that the external study conducted by (b) (4) identified (b) (4) as a potential risk. However, (b) (4) concluded that (b) (4) was well-differentiated from (b) (4) and not a valid risk due to (b) (4). However, based on our analysis, we disagree for the aforementioned reasons and conclude that these names may be confused.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- Biosimilar Biological Product Authorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM281991.pdf>)

7

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<sup>1</sup> Institute for Safe Medication Practices. Safety briefs: Advair-Advicor mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2003; 2(8): 1Institute for Safe Medication Practices. Errors and near misses prompt warning to practitioners and a call to rename CELEBREX. ISMP Med Saf Alert Acute Care. 1999;4(7):1.

(b) (4)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Neil Vora, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-4845. For any other information regarding this application, contact Leila Hann, Regulatory Project Manager in the Office of New Drugs, at 301-796-3367.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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TODD D BRIDGES  
10/26/2015



BLA 761042

**FILING COMMUNICATION -  
FILING REVIEW ISSUES IDENTIFIED**

Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540

Attention: Zhengyu (Eddy) Liu, Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Liu:

Please refer to your Biologics License Application (BLA) dated July 30, 2015, received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015.

GP2015 is a proposed biosimilar to Enbrel (etanercept) (BLA 103795).

We also refer to your amendment dated September 10, 2015.

We refer to the September 28, 2015 filing notification letter informing you that your 351(k) BLA has been accepted for review with a standard review classification and a May 30, 2015 user fee goal date.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 19, 2016.

We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. You have submitted data from two, two-way crossover studies (Studies 101 and 102) and a cross-study analysis (Report 105) to establish the PK portion of the scientific bridge between EU-approved Enbrel, US-licensed Enbrel, and GP2015; this is in lieu of the

FDA recommended three-way crossover PK similarity study. The acceptability of your approach and the PK portion of the scientific bridge in order to rely on data generated using EU-approved Enbrel will be a review issue.

2. We note that PK similarity was not demonstrated when comparing GP2015 to EU-approved Enbrel based on the predefined similarity acceptance criterion of 80-125% (Study 101). The exposure of GP2015 is lower than EU-approved Enbrel in Study 101. However, the data from Study 302 demonstrated comparable efficacy between GP2015 and EU-approved Enbrel. Taken together, the results could imply that there could be a difference in clinical activity (i.e., higher activity with GP2015) if the exposure values of GP2015 and EU-approved Enbrel were to be similar. Provide a detailed rationale for how you have concluded that the data presented in Study 302 support a demonstration of no clinically meaningful differences between GP2015 and the US-licensed Enbrel.
3. Furthermore, you have also submitted data from one additional, two-way crossover study (Study 104) between EU-approved Enbrel and GP2015. The study results appear to support the demonstration of PK similarity between GP2015 and EU-approved Enbrel based on the PK similarity acceptance criterion of 80-125%. We note however, that the exposures of both GP2015 and EU-approved Enbrel in Study 104 are higher than in Study 101. Therefore, the results from Study 104 are difficult to reconcile with Study 101. If you believe the results of Study 104 are more relevant to a demonstration of PK similarity than the results of Study 101, provide a rationale for why you believe this is the case.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following additional information:

1. Submit the statistical analysis programs used to create the estimates and confidence intervals for the primary and key secondary analyses in Study GP15-302.

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following issues related to the format of labeling and have the following labeling comments:

1. White space should be present before each major heading in HL.
2. Initial U.S. Approval in HL must be **bolded**.
3. The Patient Counseling Information statement must include the following verbatim statement that is most applicable: **“See 17 for PATIENT COUNSELING INFORMATION and Medication Guide”**
4. The section and subsection heading in the Table of Contents (TOC) must match the section and subsection heading in the FPI.
5. 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 include the type(s) of FDA-approved patient labeling.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 12, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit

consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), 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.

We acknowledge receipt of your request for a full waiver of pediatric studies for plaque psoriasis, ankylosing spondylitis, and psoriatic arthritis for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

We acknowledge receipt of your request for a partial waiver of pediatric studies for polyarticular juvenile idiopathic arthritis for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Leila P. Hann, Senior Regulatory Project Manager, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.  
Director  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
10/09/2015



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** October 02, 2015

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Leila P. Hann <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

**Total no. of pages including cover:** 3

**Comments:**

**Document to be mailed:** YES xNO

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We refer to your original BLA submission dated July 30, 2015, the Agency's information request September 17, 2015, and your email clarifications cited below in *italics*. We have the following comments and request for response:

*Clarification #1: Does FDA require pregnancy registry program for monitoring pregnant women on etanercept product? If it is not mandatory and Sandoz does not have a pregnancy exposure surveillance program in place, can we leave this information out in our revised PI?*

**FDA Response #1:** At this time, the (b) (4) heading under the labeling subsection 8.1 Pregnancy may be omitted from the revised draft proposed labeling. We will determine whether it is necessary to establish a (b) (4) later in the review cycle for this application.

*Clarification #2: Please note that in order to maintain the current labeling approach to biosimilar products,* (b) (4)

**FDA Response #2:** The Pregnancy Lactation Labeling Rule (PLLR) went into effect on June 30, 2015. (b) (4)

Your proposed labeling does not comply with PLLR requirements; therefore, your proposed labeling approach to address PLLR is not adequate. Submit revised labeling in PLLR format as previously requested, along with your supporting data prior to Monday, October 12, 2015.

Provide an updated label by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by 5pm, EST on Monday, October 12, 2015. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ October 02, 2015  
Cleared: N. Nikolov/ October 01, 2015  
E. Radden/ October 01, 2015  
TBBS/ October 01, 2015  
ORP/J.Weiner/ October 01, 2015  
S. Barnes/ October 02, 2015  
Finalized: L. Hann/ October 02, 2015

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/s/  
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LEILA P HANN  
10/02/2015



BLA 761042

**FILING NOTIFICATION LETTER**

Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540

Attention: Zhengyu (Eddy) Liu, Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Liu:

Please refer to your Biologics License Application (BLA) dated July 30, 2015, received July 30, 2015, submitted under section 351(k) of the Public Health Service Act for GP2015.

GP2015 is a proposed biosimilar to Enbrel (etanercept) (BLA 103795).

We also refer to your amendment dated September 09, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. This filing communication constitutes the notification described in section 351(l)(2) of the Public Health Service Act that your 351(k) BLA has been accepted for review. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 30, 2016.

We plan to send a separate filing communication that provides additional information and describes any potential review issues identified during the initial filing review within 74 calendar days from the date of FDA receipt of the original submission in accordance with the performance goal established under the Biosimilar User Fee Act (BsUFA).

If you have any questions, call Leila P. Hann, Senior Regulatory Project Manager, at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Badrul A. Chowdhury, M.D., Ph.D.

Director

Division of Pulmonary, Allergy, and Rheumatology

Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/  
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BADRUL A CHOWDHURY  
09/28/2015



Food and Drug Administration  
 Center for Drug Evaluation and  
 Research  
 Office of Drug Evaluation II

**FACSIMILE TRANSMITTAL SHEET**

**DATE:** September 17, 2015

<b>To:</b> Zhengyu (Eddy) Liu, Ph.D. Manager, Regulatory Affairs	Leila P. Hann <b>From:</b> Senior Regulatory Project Manager
<b>Company:</b> Sandoz, Inc.	Division of Pulmonary, Allergy, and Rheumatology Drug Products
<b>Secure Email:</b> Zhengyu.Liu@Sandoz.com	<b>Fax number:</b> 301-796-9728
<b>Phone number:</b> 609-627-8679	<b>Phone number:</b> 301-796-3367

**Subject:** BLA 761042 (GP2015 proposed biosimilar to US-licensed Enbrel (etanercept))  
Information Request

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We have received your original BLA submission dated July 30, 2015 and have the following comments and request for response:

### **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) does not conform to the content and format requirements of the Pregnancy and Lactation Labeling Rule (PLLR) which was implemented on June 30, 2015. You must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

1. The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
2. The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
3. Regulations and related guidance documents
4. A sample tool illustrating the format for Highlights and Contents
5. The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances
6. FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Provide an updated label by email (Leila.Hann@fda.hhs.gov) or facsimile (301-796-9728), by 5pm, EST on Thursday, October 01, 2015. Your response must also be submitted formally to the BLA shortly thereafter. If you have any questions, please contact Leila P. Hann, Senior Regulatory Program Manager, at 301-796-3367.

Drafted: L. Hann/ September 09, 2015  
Cleared: S. Yim/ September 09, 2015  
E. Radden/ September 09, 2015  
TBBS/ September 10, 2015  
ORP/J.Sitlani/ September 17, 2015  
C. Ford for S. Barnes/ September 09, 2015  
Finalized: L. Hann/ September 17, 2015

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/s/  
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LEILA P HANN  
09/17/2015



BLA 761042

**BLA ACKNOWLEDGMENT**

Sandoz Inc.  
100 College Road West  
Princeton, NJ 08540

Attention: Zhengyu (Eddy) Liu, Ph.D.  
Manager, Regulatory Affairs

Dear Dr. Liu:

We have received your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: GP2015 proposed biosimilar to Enbrel (etanercept) injectable  
25 mg and 50 mg

Date of Application: July 30, 2015

Date of Receipt: July 30, 2015

Our Reference Number: BLA 761042

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Pulmonary, Allergy, and Rheumatology Products

5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

Leila P. Hann  
Senior Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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/s/  
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LEILA P HANN  
08/19/2015



PIND 114187

**MEETING MINUTES**

Sandoz, Inc.  
506 Carnegie Center  
Suite 400  
Princeton, NJ 08540

Attention: John M. Pakulski, R.Ph.  
Head Regulatory Affairs, U.S. Biopharmaceuticals

Dear Dr. Pakulski:

Please refer to your Pre-Investigational New Drug Application (PIND) file for GP2015.

We also refer to the telecon between representatives of your firm and the FDA on December 19, 2012. The purpose of the meeting was to discuss your revised statistical analysis plan for the comparative clinical study in psoriasis patients, including study endpoints and statistical methodology.

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3367.

Sincerely,

*{See appended electronic signature page}*

LEILA P. HANN  
Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology  
Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type 2  
**Meeting Category:** BPD

**Meeting Date and Time:** December 19, 2012 at 12:00 PM  
**Meeting Location:** Teleconference

**Application Number:** 114187  
**Product Name:** GP2015  
**Indication:** moderate to severe rheumatoid arthritis, moderate to severe polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, moderate to severe plaque psoriasis

**Sponsor/Applicant Name:** Sandoz, Inc.

**Meeting Chair:** Badrul A. Chowdhury, M.D., Ph.D.  
**Meeting Recorder:** Leila P. Hann

**FDA ATTENDEES**

Joan Buenconsejo, Ph.D., Team Leader, Division of Biometrics II (DBII)  
Rosemarie Neuner, M.D., M.P.H., Clinical Reviewer, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)  
Sarah Yim, M.D., Supervisory Associate Director, DPARP  
Susan Limb, M.D., Clinical Team Leader, DPARP  
Badrul Chowdhury, M.D., Ph.D., Director, DPARP  
Leila P. Hann, Regulatory Project Manager, DPARP  
Leah Ripper, Associate Director for Regulatory Affairs, Office of Drug Evaluation II  
Jay Sitlani, J.D., M.S., Senior Regulatory Counsel, Office of Regulatory Counsel  
Leah Christl, Ph.D., Associate Director for Therapeutic Biologics, Therapeutic Biologics and Biosimilars Team (TBBT), Office of New Drugs (OND)  
Neel Patel, Pharm.D., Regulatory Health Project Manager, TBBT, OND  
Sue Lim, M.D., Senior Staff Fellow, TBBT, OND  
Kathleen Fritsch, Ph.D., Biometrics Reviewer, DBIII  
David Kettl, M.D., Clinical Team Leader, Division of Dermatology and Dental Products (DDDP)  
Gary Chiang, M.D., Clinical Reviewer, DDDP  
Susan Walker, M.D., F.A.A.D., Director, DDDP  
Julie Beitz, M.D., Director, Office of Drug Evaluation III  
Victoria Kusiak, M.D., Deputy Director, Office of Drug Evaluation III

**SPONSOR ATTENDEES**

Mark McCamish, Global Head, Biopharmaceutical Development  
Ingrid Schwarzenberger, Global Head, Biopharmaceutical Regulatory Affairs  
Pascale Burtin, Global Head, Biopharmaceutical Clinical Development  
Sigrid Balsler, Head, Clinical Operations & Biostatistics  
Karsten Roth, Head, Clinical Development Hematology  
Klaus Vitzithum, Head, Regulatory Affairs  
David Nganele, Senior Program Leader, Global Project Management  
John Pakulski, Head, Regulatory Affairs  
Zhengyu Liu, Team Leader, Regulatory Affairs  
Novartis Pharma AG  
Renard Didier, Senior Expert Modeler

## 1.0 BACKGROUND

Sandoz, Inc. previously met with DPARP and DDDP on July 9, 2012 where it was agreed that an additional meeting would be granted to discuss the statistical analysis plan. A meeting request was received October 01, 2012 which was granted October 17, 2012. The majority of the meeting discussion focused on study endpoints.

FDA may provide further clarifications of, or refinements and/or changes to the advice provided based on further information provided by Sandoz as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

## 2. DISCUSSION

### 2.1. Statistical Analysis Plan – Study Endpoints

**Question 1:** Together with the primary analysis based on PASI75 and the comprehensive safety, immunogenicity, and pharmacokinetic analyses as described in the briefing book, Sandoz considers the proposed data package to be adequate and sufficient to assess the biosimilarity between GP2015 and Enbrel. Does the Agency concur?

**FDA Response to Question 1:** Your proposed study design may be adequate to evaluate clinically meaningful differences between GP2015 and US-licensed Enbrel. The primary endpoint of PASI75 response at week 12 with a proposed equivalence margin of 18% appears to be adequate. Another acceptable alternative would be to evaluate the primary endpoint at the 10 week mark. The early analysis of the primary endpoint would allow evaluation at a steeper portion of the time-response curve.

The proposed secondary endpoints are adequate; however, data sets with raw PASI scores should be submitted for each patient visit.

Alternatively, we recommend that you consider a dose response/scaling approach to your comparative clinical trial in plaque psoriasis. This approach may be more sensitive to detect clinically meaningful differences, if any, between your GP2015 product and US-licensed Enbrel and could likely lead to a smaller sample size and shorter study duration.

Additional Agency comments may be forthcoming following submission of the complete protocol and statistical analysis plan to the IND.

**Discussion:** Sandoz acknowledged that week 10 or week 8 would be possible alternative time points at which to evaluate subjects; however, the primary endpoint of PASI75 response at week 12 is in line with the EMA recommendation. Sandoz stated that they would prefer to stay with week 12 and asked if FDA found this acceptable. FDA responded that, as noted in the response provided, the proposed study design and evaluation of PASI75 at week 12 is acceptable.

The sponsor requested clarification regarding the benefits of a dose response/scaling approach. The Agency commented that a dose response/scaling model would likely be more sensitive to detecting differences between products, thereby improving assay sensitivity beyond an equivalence trial design. References for this approach would be provided in an addendum to the meeting minutes. FDA noted that the intent of the suggestion was to pose a possible alternative approach for further discussion and consideration.

[REDACTED] (b) (4)

Sandoz has not selected any US sites for their comparative clinical trial. Sandoz inquired if using the EU-approved product in the comparative clinical trial would be acceptable. FDA stated that this approach could be acceptable if justification, scientific rationale, and data to bridge to the US-licensed reference product were provided, as advised at the July 9, 2012 meeting.

Sandoz plans for the primary analysis to be performed after 12 weeks and asked if the 18 week data could be provided in a later submission. Sandoz clarified that this meant there would be no single transition data in the original BLA submission; this data would be provided in a Day 120 safety assessment, and asked if such an approach would be acceptable. FDA responded that a descriptive analysis around a single transition is necessary to support a demonstration of biosimilarity for this proposed product. These data are considered necessary for a safety assessment, and therefore the 12 week safety data would not be adequate. The Agency expects the BLA to be complete at the time of submission, which would include the single transition safety data. FDA clarified that single transition data is considered part of the biosimilarity assessment, and not for an assessment of interchangeability.

Lastly, Sandoz inquired if the current study design, which proposes to transition 50% of patients on EU-approved etanercept to GP2015, was acceptable to the Agency. FDA responded that acceptability would depend on the immunogenicity data submitted. Sandoz should estimate the number of patients necessary to detect anaphylaxis and hypersensitivity based on the incidence of this adverse event reported with etanercept. Depending on the incidence rate, 50-100 patients per arm may be acceptable to provide a descriptive analysis of safety. Sandoz plans to discuss the immunogenicity data during a pre-filing meeting.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues requiring further discussion were identified during the meeting.

### **4.0 ACTION ITEMS**

FDA agreed to provide references on the dose response/scaling approach which are included as an attachment.

### **5.0 ATTACHMENTS AND HANDOUTS**

The first attachment below was provided by John Pakulski of Sandoz via email on December 18, 2012. The second and third attachments are the references on the dose response/scaling approach.

15 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

**Bioequivalence (BE) Assessment  
Based on  
Pharmacodynamic (PD) Response**

**BE Criteria on the Dose Scale:  
Rationale, Theory and Methods**

**William R. Gillespie  
Office of Clinical Pharmacology and  
Biopharmaceutics  
Center for Drug Evaluation and Research  
Food and Drug Administration**

**Joint Session of the  
Advisory Committee for Pharmaceutical Science  
and the  
Pulmonary-Allergy Drugs Advisory Committee  
Holiday Inn, Gaithersburg, MD  
August 16, 1996**

# **BE Criteria on the Dose Scale: Rationale, Theory and Methods**

## **Objective**

General description of the dose scale approach for BE assessment based on PD response measurements.

## **Outline**

- **Rationale**
  - ▶ Conceptual and philosophical arguments in support of the dose scale approach.
- **Theory**
  - ▶ Non-mathematical presentation of the basic principles used in dose scale BE assessment.
- **Methods**
  - ▶ Study design requirements.
  - ▶ Brief non-mathematical description of the data analysis tasks required for the dose scale approach.

# **BE Criteria on the Dose Scale**

## **Rationale**

**Equivalence of the amount of drug that reaches the site of action<sup>1</sup> is a better surrogate for therapeutic equivalence than equivalence of a single PD measure.**

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<sup>1</sup> or a post-absorptive precursor site, e.g., the general circulation for systemically administered drugs.

# **Additional Arguments for Dose Scale BE**

- **Generalizable to other products and PD responses.**
  - ▶ E.g., other MDI's and topicals.
  - ▶ E.g., bronchodilation (FEV1) or bronchoprotection (PC20).
- **Can provide a general theoretical and methodological framework for BE assessment using PD measurements.**
  - ▶ Less time and expense for establishing methods and requirements for other products.
  - ▶ Enhanced consistency and defensibility.
- **Consistent with existing BE methods and criteria based on PK measurements.**

# BE Criteria on the Dose Scale

## Theory

Reference product dose-response data



Dose-response curve

+

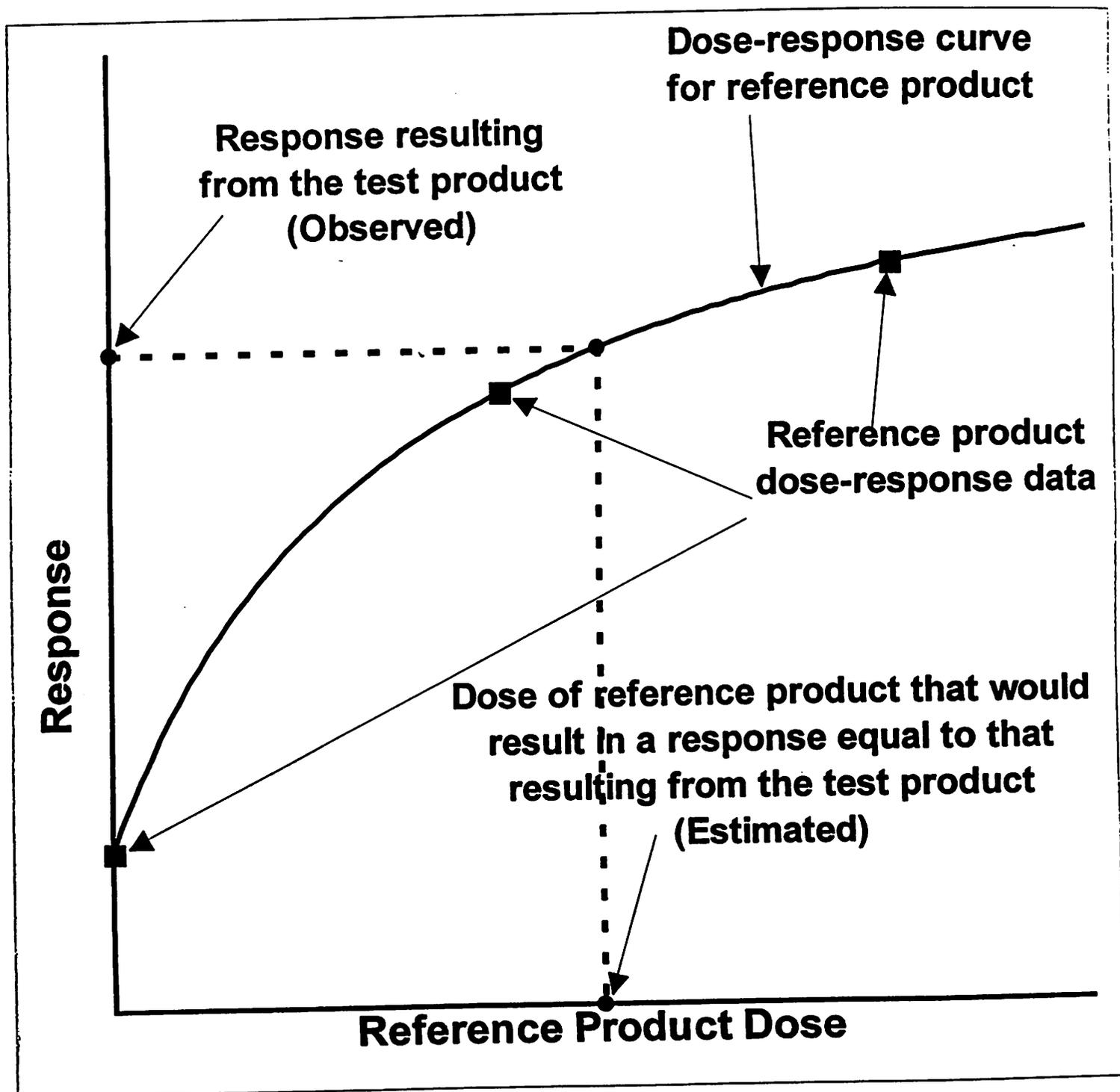
Test product data



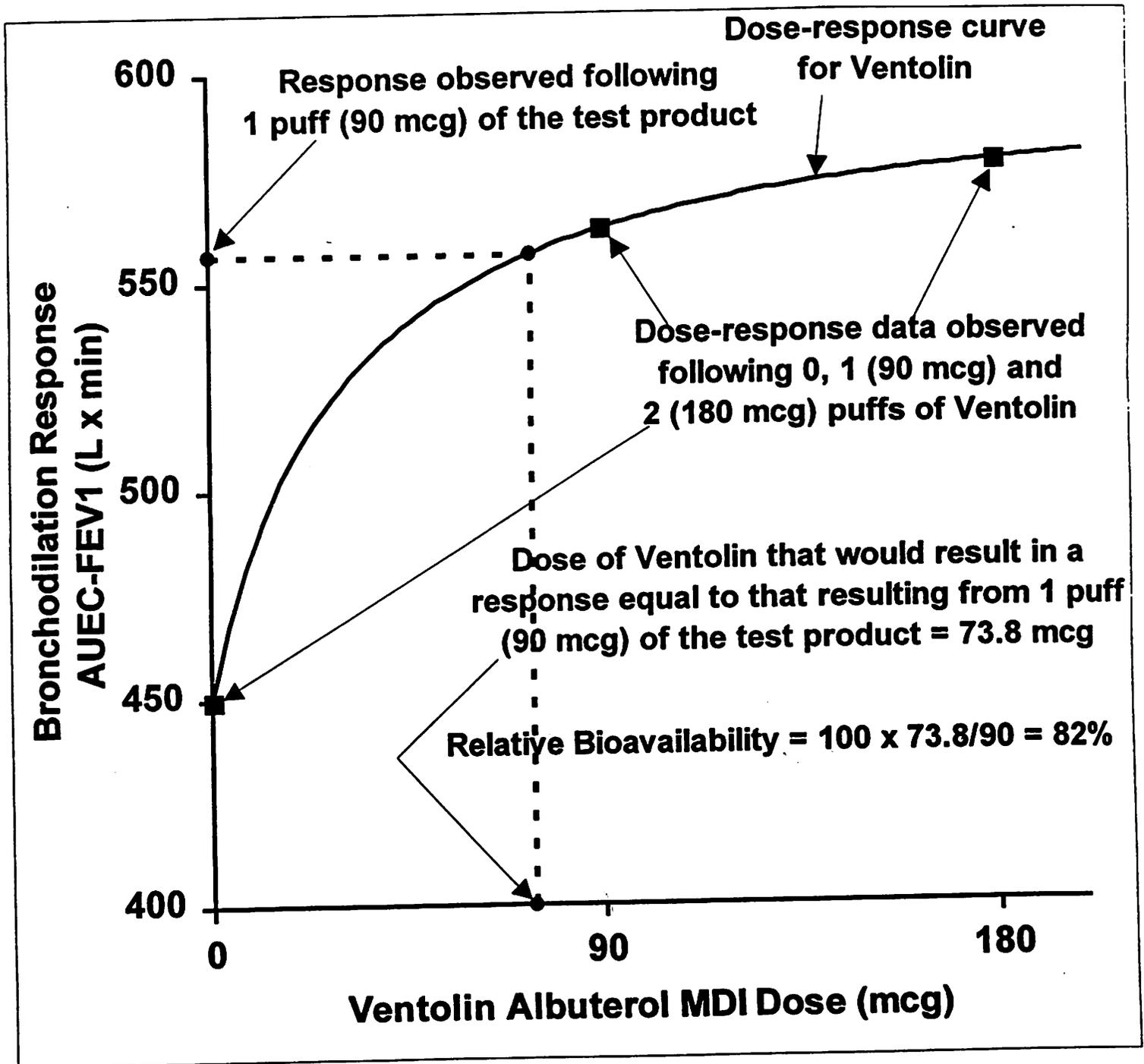
Dose of reference product that would result in a response equal to that resulting from the test product ("equipotent reference product dose")

$$\text{Relative Bioavailability} = \frac{\text{Equipotent reference product dose}}{\text{Test product dose}}$$

# BE Criteria on the Dose Scale: Theory



# Application of the Dose Scale Approach to Albuterol MDI's (hypothetical example)



# **BE Criteria on the Dose Scale**

## **Basic Study Design**

- **Test Product**
  - ▶ **One dose level, e.g., 1 puff of a generic albuterol MDI.**
  
- **Reference Product**
  - ▶ **Two dose levels, e.g., 1 and 2 puffs of Ventolin.**
  
- **Measure of zero dose response**
  - ▶ **Placebo or baseline**
  
- **Crossover or parallel**

# **Acknowledgements**

## **PD/BE Working Group**

**Technical team for developing the dose scale concept and methodology:**

- **William Gillespie**
- **Stella Machado**
- **Don Schuirmann**
- **Ray Zhu**

**Influences for the dose scale concept:**

- **Current**
  - ▶ **Lewis Sheiner**
  - ▶ **Nicholas Holford**
- **Historical**
  - ▶ **David Finney**
  - ▶ **Victor Smolen**

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/s/  
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LEILA P HANN  
01/16/2013