

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761024Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|--|--|
| NDA # BLA # 761024 | NDA Supplement # BLA Supplement # | If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i> |
| Proprietary Name: Amjevita Established/Proper Name: adalimumab-atto Dosage Form: Subcutaneous injection | | Applicant: Amgen, Inc. Agent for Applicant (if applicable): |
| RPM: Sadaf Nabavian | | Division: Division of Pulmonary, Allergy, and Rheumatology Products |
| 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><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <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"> Proposed action User Fee Goal Date is <u>September 25, 2016</u> | | <input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> | | <input type="checkbox"/> None X |
| ❖ 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | | <input type="checkbox"/> Received |
| ❖ Application Characteristics ³ | | |

¹ 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.

² 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).

³ 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 type="checkbox"/> No <input checked="" type="checkbox"/> Yes Orphan Drug Exclusivity for the indications of pJIA, HS, and pediatric CD |
| ❖ 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. |
| CONTENTS OF ACTION PACKAGE | |
| Officer/Employee List | |
| ❖ 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 |

| Action Letters | |
|---|---|
| ❖ Copies of all action letters <i>(including approval letter with final labeling)</i> | Action(s) and date(s) September 23, 2016 |
| Labeling | |
| ❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i> | |
| <ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> | <input checked="" type="checkbox"/> Included (as enclosed to the action letter) |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | <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"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> | <input checked="" type="checkbox"/> Included (as enclosed with the action letter) |
| <ul style="list-style-type: none"> Original applicant-proposed labeling | <input checked="" type="checkbox"/> Included |
| ❖ Labels (full color 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"> Most-recent draft labeling | <input checked="" type="checkbox"/> Included |
| ❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> | 8/19/2016 and 8/15/2016 |
| ❖ Labeling reviews <i>(indicate dates of reviews)</i> | RPM: <input checked="" type="checkbox"/> 2/5/2016 None DMEPA: <input checked="" type="checkbox"/> 9/15/2016, 8/11/2016 None DMPP/PLT (DRISK): <input checked="" type="checkbox"/> 8/23/2016 None OPDP: <input checked="" type="checkbox"/> 8/31/2016 None SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> 9/22/16 None Other: <input checked="" type="checkbox"/> DPMH 8/19/2016 None |
| Administrative / Regulatory Documents | |
| ❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i> | Filing Review: 2/5/2016 |
| ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee | <input type="checkbox"/> Not a (b)(2) |
| ❖ NDAs/NDA supplements only: Exclusivity Summary <i>(signed by Division Director)</i> | <input type="checkbox"/> Completed |

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

| | |
|---|---|
| ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> • Applicant is on the AIP | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action |
| ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>July 27, 2016</u> If PeRC review not necessary, explain: _____ | |
| ❖ Breakthrough Therapy Designation | <input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) | |
| <ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) | |
| <ul style="list-style-type: none"> • 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>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p> | |
| ❖ 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>) | 9/22/16, 9/9/15/16 (2), 9/13/16, 9/12/16, 9/9/16, 9/7/16, 8/31/16, 8/24/16 8/17/16, 8/16/16, 8/12/16 (2), 8/11/16, 8/9/16, 7/29/16, 7/28/16 (3), 7/27/16, 7/21/16 (2), 7/18/16, 6/30/16, 6/22/16, 6/7/16, 5/19/16, 5/9/16, 5/4/16, 3/30/16, 3/21/16, 3/4/16 (2), 2/8/16 2/5/16 and 1/22/16, 12/24/15, 12/9/2015 |
| ❖ 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) | 9/13/16, 9/9/16, 8/9/16, 6/7/2016, 3/4/16, 1/6/2016 |
| ❖ Minutes of Meetings | |
| <ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> N/A or no mtg |
| <ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> August 7, 2015 No mtg |
| <ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) | <input type="checkbox"/> No mtg |
| <ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) | <input type="checkbox"/> 4/5/2016 N/A |
| <ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) | <input checked="" type="checkbox"/> N/A |
| <ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) | |

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|--|--|
| ❖ Advisory Committee Meeting(s) | <input type="checkbox"/> No AC meeting |
| • Date(s) of Meeting(s) | July 12, 2016 |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) | <input type="checkbox"/> None |
| Division Director Summary Review (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> 9/23/2016 None |
| Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) | <input checked="" type="checkbox"/> 9/23/2016 None |
| PMR/PMC Development Templates (<i>indicate total number</i>) | <input checked="" type="checkbox"/> 6 None |
| Clinical | |
| ❖ 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>) | DGIEP: 9/15/16 DPAAP: 9/7/2016; 2/1/2016 DDDP: 1/8/2016 |
| • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) | <input 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>) | Clinical Review dated 9/7/2016, page 25 and form completed 9/22/16. |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵ | <input type="checkbox"/> 9/22/16 (2) None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>) | <input type="checkbox"/> N/A |
| ❖ Risk Management | |
| • REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) | |
| • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) | |
| • 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>) | <input type="checkbox"/> None |
| ❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>) | <input checked="" type="checkbox"/> 8/24/2016, 7/15/16 None requested |

⁵ 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).

| Clinical Microbiology <input checked="" type="checkbox"/> None | |
|--|--|
| ❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review) | <input type="checkbox"/> No separate review |
| Clinical Microbiology Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (indicate date for each review) | <input type="checkbox"/> No separate review |
| Statistical Team Leader Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> 9/15/16, 9/7/2016, 9/15/16, 1/11/16 (2) No separate review |
| Statistical Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review) | <input type="checkbox"/> No separate review |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review) | <input type="checkbox"/> No separate review |
| Clinical Pharmacology review(s) (indicate date for each review) | <input checked="" type="checkbox"/> 8/18/2016;1/22/3016 None |
| ❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters) | <input checked="" type="checkbox"/> 7/27/2016; 7/21/2016, 6/7/16, 3/4/16 ; None requested |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (indicate date for each review) | <input type="checkbox"/> No separate review |
| • Supervisory Review(s) (indicate date for each review) | <input checked="" type="checkbox"/> 8/29/16 No separate review |
| • Pharm/tox review(s), including referenced IND reviews (indicate date for each review) | <input checked="" type="checkbox"/> 9/20/16, 8/22/16, 1/12/2016 None |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review) | <input type="checkbox"/> None |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review) | <input type="checkbox"/> No carc |
| ❖ ECAC/CAC report/memo of meeting | <input type="checkbox"/> None Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters) | <input type="checkbox"/> None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews ⁶ | |
| • Tertiary review (indicate date for each review) | <input type="checkbox"/> None |
| • Secondary review (e.g., Branch Chief) (indicate date for each review) | <input checked="" type="checkbox"/> 9/8/16 None |
| • Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review) | <input checked="" type="checkbox"/> 9/7/16, 8/23/16, 1/13/16 None |
| ❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review) | <input checked="" type="checkbox"/> 9/20/16, 8/31/2016, 8/29/2016 (2) , CMC Stats 8/17/16 |

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

| | |
|--|--|
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | 8/23/16: CMC Review, Pg. 7 |
| <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 checked="" type="checkbox"/> Facilities inspections (<i>indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation</i>) (<i>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 |

| Day of Approval Activities | |
|---|--|
| ❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>) |
| <ul style="list-style-type: none"> • Finalize 505(b)(2) assessment | <input type="checkbox"/> Done |
| ❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager | <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): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications | <input type="checkbox"/> Done |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | <input checked="" 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 checked="" 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 checked="" type="checkbox"/> Done |
| ❖ Ensure Pediatric Record is accurate | <input checked="" type="checkbox"/> Done |
| ❖ Send approval email within one business day to CDER-APPROVALS | <input checked="" type="checkbox"/> Done |

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

/s/

SADAF NABAVIAN
09/26/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) Biologics License Application (BLA) 761024, submitted on November 25, 2015, is currently under review. We are providing our labeling comments and recommendations listed below and in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling recommendations are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

We have the following comments regarding your proposed container labels and carton labeling attached to your email correspondence to Ms. Sadaf Nabavian on September 15, 2016.

A. Carton Labeling (All package sizes; Prefilled syringe: 20 mg/0.4 mL and 40 mg/0.8 mL mg; SureClick Autoinjector)

1. Revise the strength presentation on the carton labeling similar to other Amgen products such as Repatha (evolocumab), Blincyto (blinatumomab), and Neulasta Onpro (pegfilgrastim).

40 mg/
0.8 mL

or

40 mg/
0.8 mL

B. General Comment

1. Your previous container label and carton labeling response did not contain all the different presentations. We note that all the (b) (4) were not submitted. Confirm if you plan to market all the presentations included in section 16 How Supplied/Storage and Handling, of the the package insert (PI). If so, submit all container labels and labeling in your response. Otherwise, remove any packaging presentation that you do not intend to market from the How Supplied section of the PI.

Submit revised labeling incorporating the changes shown in the attached marked up labels via email to Sadaf.Nabavian@fda.hhs.gov by noon Tuesday, September 20, 2016, followed by official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/9.16.2016

Cleared by: LJafari/9.16.2016

TBBS/9.16.2016

OCC/9.16.2016

Finalized by: SNabavian/9.19.2016

62 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

SADAF NABAVIAN
09/19/2016



BLA 761024

GENERAL ADVICE

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for ABP 501.

We also refer to:

- Your correspondence, dated and received August 12, 2016, containing your request for review of the proposed suffixes for the nonproprietary name of your proposed product.
- FDA's response, sent September 7, 2016, regarding the proposed suffixes.
- The teleconference between FDA and Amgen, held September 8, 2016, regarding the proposed suffixes.
- Your correspondence, dated and received September 13, 2016, containing additional analyses pertaining to the proposed suffixes.

We have reviewed the submission and have the following comments:

We find the nonproprietary name, adalimumab-atto, conditionally acceptable for your proposed product. Adalimumab-atto, 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.

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 Sadaf Nabavian, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2777.

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

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

/s/

KELLIE A TAYLOR
09/15/2016

Harris, Sarah

From: Sinks, Michael
Sent: Thursday, September 15, 2016 3:14 PM
To: 'kamassah@amgen.com'
Cc: Rashid, Nichelle E; Nabavian, Sadaf; Harris, Sarah
Subject: BLA 761024 - Proposed suffixes for Nonproprietary Name General Advice Correspondence
Attachments: BLA 761024 ABP501 Proper Name Conditionally Acceptable General Advice Letter.pdf
Categories: DPARP

Dear Mr. Kamassah,

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for ABP501.

We also refer to your August 12, 2016, submission, containing your request for review of the proposed suffixes for the nonproprietary name of your proposed product. We also make reference to your correspondence, dated and received September 13, 2016, containing additional analyses pertaining to the proposed suffixes. Attached you will find a courtesy copy of the Agency's correspondence, sent via mail today.

If you have any questions, please don't hesitate to contact me.

Kind Regards,

Michael Sinks, Pharm. D.

FDA Project Manager

Office of Surveillance and Epidemiology

Office Phone: (240)402-2684

Work Cell: (b) (6)

Email: Michael.Sinks@FDA.hhs.gov

From: Kamassah, Augustus [<mailto:kamassah@amgen.com>]
Sent: Wednesday, September 07, 2016 7:06 PM
To: Sinks, Michael
Cc: Rashid, Nichelle E; Harris, Sarah; Nabavian, Sadaf
Subject: RE: BLA 761024 - Proposed suffixes for Nonproprietary Name General Advice Correspondence

Hello Michael,

This is to acknowledge receipt of the FDA General Advice correspondence on the proposed suffixes for the nonproprietary name of ABP 501.

I would like to confirm that the Amgen team would still like to meet tomorrow afternoon.

The dial-in information is:

Call-in toll-free number: (b) (4)

Call-in number: (b) (4)

Conference Code (b) (4)

Regards,
Augustus

From: Sinks, Michael [<mailto:Michael.Sinks@fda.hhs.gov>]
Sent: Wednesday, September 07, 2016 12:46 PM
To: Kamassah, Augustus
Cc: Rashid, Nichelle E; Harris, Sarah; Nabavian, Sadaf
Subject: BLA 761024 - Proposed suffixes for Nonproprietary Name General Advice Correspondence

Dear Mr. Kamassah,

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for ABP501.

We also refer to your August 12, 2016, submission, containing your request for review of the proposed suffixes for the nonproprietary name of your proposed product. Attached you will find a courtesy copy of the correspondence, sent via mail today. Please confirm if Amgen would still like to meet tomorrow afternoon.

If you have any questions, please don't hesitate to contact me.

Kind Regards,

Michael Sinks, Pharm. D.
FDA Project Manager
Office of Surveillance and Epidemiology
Office Phone: (240)402-2684
Work Cell: (b) (6)
Email: Michael.Sinks@FDA.hhs.gov

From: Kamassah, Augustus [<mailto:kamassah@amgen.com>]
Sent: Wednesday, September 07, 2016 9:47 AM
To: Harris, Sarah
Cc: Nabavian, Sadaf; Sinks, Michael
Subject: RE: BLA 761024 - Proposed suffixes for Nonproprietary Name (re 10 August 2016 teleconference)

Hello Sarah,

Thanks for your call this morning. This is to acknowledge receipt of your email and we look forward to receiving the feedback from the FDA .

Regards,
Augustus

From: Harris, Sarah [<mailto:Sarah.Harris@fda.hhs.gov>]
Sent: Tuesday, September 06, 2016 8:49 AM
To: Kamassah, Augustus
Cc: Nabavian, Sadaf; Sinks, Michael
Subject: RE: BLA 761024 - Proposed suffixes for Nonproprietary Name (re 10 August 2016 teleconference)

Hi Augustus,

This is to inform you that FDA plans to provide feedback on your proposed proper name suffixes for BLA 761024 shortly. We have identified some issues with the proposals, and therefore have set aside time on Thurs 9/8/16 from 4:00PM – 4:300PM EST for discussion to take place, if needed. After receiving our feedback (via electronic copy), please confirm whether you would like to speak and if so, provide a call-in number.

Kind Regards,
Sarah

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

From: Harris, Sarah
Sent: Monday, August 15, 2016 9:43 AM
To: 'Kamassah, Augustus'
Cc: Nabavian, Sadaf; Sinks, Michael
Subject: RE: BLA 761024 - Proposed suffixes for Nonproprietary Name (re 10 August 2016 teleconference)

Thank you for confirming, Augustus.

Best,
Sarah

From: Kamassah, Augustus [<mailto:kamassah@amgen.com>]
Sent: Friday, August 12, 2016 6:52 PM
To: Harris, Sarah
Cc: Nabavian, Sadaf; Sinks, Michael
Subject: RE: BLA 761024 - Proposed suffixes for Nonproprietary Name (re 10 August 2016 teleconference)

Hello Sarah,

The formal submission of the email communication regarding the proposed suffixes (emailed on 10 August) was made to BLA 760124 today under SN 0031.

Regards,
Augustus

From: Harris, Sarah [<mailto:Sarah.Harris@fda.hhs.gov>]
Sent: Thursday, August 11, 2016 5:35 AM
To: Kamassah, Augustus
Cc: Nabavian, Sadaf; Sinks, Michael
Subject: RE: BLA 761024 - Proposed suffixes for Nonproprietary Name (re 10 August 2016 teleconference)

Good Morning Augustus,
Thanks very much for quickly confirming these 3 proposed suffixes. I have distributed to the team to begin assessment.

We will look out for a formal submission to the BLA to follow.

Kind Regards,
Sarah

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

From: Kamassah, Augustus [<mailto:kamassah@amgen.com>]
Sent: Wednesday, August 10, 2016 8:55 PM
To: Harris, Sarah
Cc: Nabavian, Sadaf
Subject: BLA 761024 - Proposed suffixes for Nonproprietary Name (re 10 August 2016 teleconference)

Hello Sarah,

Thanks for the time opportunity to meet with your team via teleconferencing this afternoon (10 August 2016) to discuss Amgen's proposed suffixes for the Nonproprietary Name.

As discussed on the call, these are the proposed suffixes in order of preference.

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

These suffixes will be submitted formally to the BLA.

We look forward to your feedback.

Regards,
Augustus

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/s/

SARAH J HARRIS
09/15/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) Biologics License Application (BLA) 761024, submitted on November 25, 2015, is currently under review. We request that you provide your agreement to the following deferred Pediatric Research Equity Act (PREA) postmarketing requirements (PMR) outlined below. We request you propose a Final Report Submission date and provide a rationale for the proposed milestone for each PMR. We note that as we continue our review of your 351(k) BLA, additional post-marketing requirements/commitments may be conveyed to you.

1. Assessment of [ABP-TRADENAME] adalimumab-xxxx for the treatment of pediatric ulcerative colitis in patients 5 to 17 years of age.

Final Report Submission Date: Month/Year

2. Assessment of [ABP-TRADENAME] adalimumab-xxxx for the treatment of pediatric Crohn's disease in patients 6 years to 17 years of age.

Final Report Submission Date: Month/Year

3. Assessment of [ABP-TRADENAME] adalimumab-xxxx for the treatment of juvenile idiopathic arthritis (JIA) in patients ages 2 to <4 years of age.

Final Report Submission Date: Month/Year

4. Develop a presentation that can be used to accurately administer [ABP-TRADENAME] adalimumab-xxxx to pediatric patients who weigh less than 15 kg.

Final Report Submission Date: Month/Year

Submit your responses via email to Sadaf.Nabavian@fda.hhs.gov by close of business, September 15, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/9.8.2016

Cleared by: LJafari/9.8.2016

KHull/NNikolov/9.9.2016; 9.12.2016

CHill/SSeymour/9.9.2016

TBBS/9.12.2016

DPMH/9.13.2016

Finalized by: SNabavian/9.13.2016

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/s/

SADAF NABAVIAN
09/13/2016

MEMORANDUM OF MEETING MINUTES

Meeting Type: Teleconference
Meeting Date and Time: Thursday September 8, 2016
Meeting Location: Bldg 22 Rm 3376
Application Number: BLA 761024
Product Name: ABP501 (adalimumab, proposed biosimilar to US-licensed Humira®)
Indication: Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis.
Sponsor/Applicant Name: Amgen
Meeting Chair: Kellie Taylor
Meeting Recorder: Sarah Harris

FDA ATTENDEES

Kellie Taylor, PharmD MPH, Deputy Director, OMEPRM/Office of Surveillance and Epidemiology (OSE)
Sue Lim, MD, TBBS/OND
Patrick Raulerson, Senior Regulatory Counsel, Office of Regulatory Policy (ORP), CDER
Sandra Benton, Senior Policy Analyst, Office of Medical Policy
Jennifer Schwartz, Office of Chief Council (OCC)
Lubna Merchant, Deputy Director, Division of Medication Errors Prevention and Analysis (DMEPA)
Carlos Mena Grillasca, Safety Evaluator, DMEPA
Diane Maloney, JD, Associate Director for Policy CBER
Sarah Harris, PharmD, Safety Regulatory Project Manager (SRPM), OSE
Michael Sinks, PharmD, SRPM, OSE
Nichelle Rashid, PharmD. SRPM Team Leader, OSE
Nikolay Nikolov, MD, Division of Pulmonary, Rheumatology, and Allergy Products (DPARP)

SPONSOR ATTENDEES

Simon Hotchin, Executive Director, Global Biosimilars Regulatory Affairs, CMC
Primal Kaur, MD, MBA, Executive Medical Director, Biosimilars Development
Augustus Kamassah, MS, Senior Manager, Global Biosimilars Regulatory Affairs
Diana Landa, MS, Director, Global Biosimilars Regulatory Affairs
Richard Markus, MD, PhD, Vice President, Biosimilars Development

BACKGROUND

On August 8, 2016, FDA sent Amgen feedback on their three proposed suffixes. The purpose of the meeting was to discuss this feedback and outline the path forward on the nonproprietary name for ABP501.

DISCUSSION

Amgen acknowledged receipt of FDA's letter outlining concerns with the proposed suffix. Amgen indicated they had conducted an analysis of the issues, and felt the identified concerns regarding the abbreviations would be unlikely to result in medication errors. Amgen offered to provide this to FDA for their consideration. FDA inquired if Amgen had conducted practitioner surveys of the suffix, and Amgen indicated they had not done so but had conducted other relevant searches and analyses. FDA stated that a data-driven argument would be most compelling but that we would review any information provided by Amgen to support their suffix candidates.

FDA reminded Amgen that FDA had also identified a potential trademark issue with their proposed -atto suffix. Amgen indicated their own legal analysis failed to identify this issue and that they would provide that to us for our review and consideration.

Amgen further confirmed that they had no additional suffix candidates to submit at this time beyond the original candidates proposed.

Amgen agreed to provide additional information as quickly as possible, and FDA indicated they would work quickly in their review and keep Amgen apprised of the findings and timelines for review completion.

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/s/

SARAH J HARRIS
09/13/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) Biologics License Application (BLA) 761024, submitted on November 25, 2015, is currently under review. We are providing our labeling comments and recommendations in the attached label. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling recommendations are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

Submit revised labeling incorporating the changes shown in the attached marked up labels via email to Sadaf.Nabavian@fda.hhs.gov by COB Wednesday, September 14, 2016, followed by official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/9.7.2016

Cleared by: LJafari/9.9.2016
TBBS/8.24.2016; 9.9.2016

Finalized by: SNabavian/9.9.2016

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
immediately following this page

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/s/

SADAF NABAVIAN
09/12/2016

MEMORANDUM OF MEETING MINUTES

Meeting Type: Teleconference
Meeting Date and Time: Wednesday August 10, 2016
Meeting Location: Bldg 22 Rm 2376
Application Number: BLA 761024
Product Name: ABP501 (adalimumab, proposed biosimilar to US-licensed Humira®)
Indication: Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Plaque Psoriasis.
Sponsor/Applicant Name: Amgen
Meeting Chair: Kellie Taylor
Meeting Recorder: Sarah Harris

FDA ATTENDEES

Kellie Taylor, PharmD MPH, Deputy Director, OMEPRM/Office of Surveillance and Epidemiology (OSE)
Leah Christl, PhD, Associate Director for Therapeutic Biologics, TBBS/OND
Sue Lim, MD, TBBS/OND
Steve Kozlowski, MD, Office of Biotechnology Products
Patrick Raulerson, Senior Regulatory Counsel, Office of Regulatory Policy (ORP), CDER
Sandra Benton, Senior Policy Analyst, Office of Medical Policy
Lubna Merchant, Deputy Director, Division of Medication Errors Prevention and Analysis (DMEPA)
Carlos Mena Grillasca, Safety Evaluator, DMEPA
Danielle Harris, Safety Evaluator, DMEPA
Bob Ball, Deputy Director, OSE
Yana Mille, RPh, Pharmacologist, Office of Policy for Pharmaceutical Quality, OPQ
Diane Maloney, JD, Associate Director for Policy CBER
Sarah Harris, PharmD, Safety Regulatory Project Manager, OSE
Michael Sinks, PharmD, Safety Regulatory Project Manager, OSE
Nikolay Nikolov, MD, Division of Pulmonary, Rheumatology, and Allergy Products (DPARP)

SPONSOR ATTENDEES

Simon Hotchin, Executive Director, Global Biosimilars Regulatory Affairs, CMC
Primal Kaur, MD, MBA, Executive Medical Director, Biosimilars Development
Augustus Kamassah, MS, Senior Manager, Global Biosimilars Regulatory Affairs
Diana Landa, MS, Director, Global Biosimilars Regulatory Affairs
Richard Markus, MD, PhD, Vice President, Biosimilars Development

BACKGROUND

FDA received Amgen's submission dated July 29, 2016 responding to our information request dated July 19, 2016. The purpose of the meeting was to outline the path forward on the nonproprietary name for ABP501.

DISCUSSION

- Kellie Taylor led the discussion, confirming that FDA received the Amgen response and appreciates the efforts Amgen made in trying to develop three suffixes that follow the principles outlined in Section V of FDA's draft guidance on Nonproprietary Naming of Biological Products.
- FDA conducted analyses of Amgen's proposed suffixes and identified concerns that render the suffixes non-viable. These include:
 - The suffix should be devoid of meaning (see line 364)
 - [REDACTED] (b) (4)
[REDACTED] Thus we determine that this suffix is not consistent with our current draft guidance or our request for suffixes that are devoid of meaning.
 - Look similar to or be mistaken for the name of a currently marketed product (e.g., should not increase the risk of confusion or medical errors with the product and/or other products in the clinical setting [line 376-377])
 - Your proposed suffix – [REDACTED] (b) (4) contains [REDACTED] (b) (4) the abbreviation for [REDACTED] (b) (4) [REDACTED] which is still an active NDA.
 - Additionally, both [REDACTED] (b) (4), and [REDACTED] (b) (4) return live trademarks from USPTO. If FDA were to proceed further in evaluations we would ask that Amgen conduct due diligence on the proposed suffixes to ensure that no other restrictions apply to the proposed suffix's use in the context of the nonproprietary name (line 382).
- FDA affirmed that we are eager to work with Amgen given the rapid approach of the goal date for their pending 315(k) BLA.
- FDA requests that Amgen submit additional non-meaningful suffixes for consideration as soon as possible.
- Amgen confirmed that they will submit a new proposal for suffixes as soon as possible via email and then via official submission.

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/s/

SARAH J HARRIS
09/09/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) Biologics License Application (BLA) 761024, submitted on November 25, 2015, is currently under review. We are providing our labeling comments and recommendations listed below and in the attached marked up labeling. The proposed insertions are (underlined) and deletions are in (strike-out). Be advised that these labeling recommendations are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming.

We have the following comments regarding your proposed container labels and carton labeling:

A. General Comments

1. Update the trade name on the container labels and carton labeling to display Amjevita instead of Trade Name.
2. Indicate how the label is affixed to the prefilled syringe and SureClick Autoinjector and where the visual area of inspection is located per 21 CFR 610.60(e).

B. All container labels and labeling

1. Ensure the presentation of the proper name is at least ½ the size of the trade name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). As currently presented, the trade name placeholder and proper name –XXXX are not commensurate in prominence due to the larger font size used for the trade name placeholder.
2. (b) (4) only the actual net content (i.e. 20 mg/0.4 mL or 40 mg/0.8 mL) is required on the labels per USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drugs Products.

Increase the prominence of the middle digits of the NDC numbers by increasing their size in comparison to the remaining digits in the NDC and by bolding (for example: xxxxx-**XXX**-xx). The similarity of the product code numbers has led to selecting and dispensing errors. The middle digits of the NDC number are traditionally used by healthcare providers to check the correct product, strength, and formulation.

C. Container Labels (Prefilled syringe: 20 mg/0.4 mL and 40 mg/0.8 mL)

1. Revise the strength statement so that it is presented only once as “20 mg/0.4 mL” or 40 mg/0.8 mL” to prevent clutter and improve legibility on these small labels. For this single-dose injectable drug product, the strength per total volume should be the primary and prominent expression on the principal display panel (PDP) of the label. For containers holding a volume of less than 1 mL, the strength per fraction of a mL should be the only expression of strength per USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drugs Products.
2. Reduce the prominence of the “Rx Only” statement by un-bolding and reducing the size of the font. As currently presented it is more prominent than more relevant information such as the proper name.

D. Container Label (Prefilled syringe: 20 mg/0.4 mL)

1. Revise the color scheme presentation for the strength statements (i.e. font color over color blocking) to increase contrast and legibility. As currently presented, the contrast between the light blue font and the orange color blocking is difficult to read.

E. Container Labels (SureClick Autoinjector)

1. Revise the light blue color font used for most of the information presented on this label to a darker color to improve contrast and legibility. As currently presented, the contrast between the light blue font and white background make the label difficult to read.
2. Revise the strength statement so that it is presented only once as “40 mg/0.8 mL” to prevent clutter and improve legibility on these small labels. Consider relocating “Single-Use” from next to the strength statement to appear under the route of administration.
3. Relocate the statement “SureClick Prefilled Autoinjector” below the strength statement.

F. Carton labeling (All package sizes; Prefilled syringe: 20 mg/0.4 mL and 40 mg/0.8 mL mg; SureClick Autoinjector)

1. As currently presented, “Injection” appears obstructed by the blue and yellow graphic next to the proper name “adalimumab-xxxx^{*}”. Revise the blue and yellow graphic so that “Injection” can appear in its customary presentation centered or left justified under the proper name.
2. Revise the strength statement that appears next to the ^{(b) (4)} image representing the prefilled syringe or autoinjector ^{(b) (4)} to read “20 mg/0.4 mL” or “40 mg/0.8 mL”.
3. Delete the strength statement on the side panels or consider adding the proprietary name, proper name, and dosage form along with strength in the customary presentation.

Amjevita
adalimumab-xxxx^{*}
Injection
40 mg/0.8 mL

4. Revise the storage statement on the Principal Display Panel to read “Store refrigerated at...”.
5. Revise the list of ingredients to be consistent with the *Description and Composition of the Drug Product* submitted in the BLA. Additionally, list the names of the inactive ingredients in alphabetical order per USP, General Chapters: <1091> Labeling of Inactive Ingredients. Additionally, For example: Each single-use prefilled syringe delivers x mL containing x mg adalimumab-xxxx^{*}, glacial acetic acid (x mg), polysorbate 80 (x mg), sodium hydroxide for pH adjustment, sucrose (x mg), and Water for Injection, USP.
6. Relocate the manufacturer information from the crowded PDP to a side or back panel.
7. Relocate the license number to appear with the manufacturer name and address per 21 CFR 610.61(b).
8. Consider revising the schematic image of the prefilled syringe and Sureclick Autoinjector by utilizing a more accurate image or photo.

^{*} FDA is using “-xxxx” as a placeholder for the suffix. The suffix for the nonproprietary name for Amjevita has not been determined. -xxxx is not intended to be included in your final printed labels and labeling.

G. Carton labeling (Prefilled syringe: 20 mg/0.4 mL carton of 1 and 40 mg/0.8 mL carton of 1 and carton of 2; SureClick Autoinjector carton of 1 and carton of 2)

1. Revise the patient/caregiver storage instructions on the side panel to read Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. If needed, Amjevita may be kept at room temperature up to 77°F (25°C) in the original carton and must be used within 14 days. (b) (4)
date removed from the refrigerator.

____/____/____
Note replacement (b) (4) with “ ____ / ____ / ____ ” to allow users to fill in the actual date. Additionally, confirm the (b) (4) distribution cartons will not be dispensed to patients (b) (4)

H. Carton Labeling (Prefilled syringe, All package sizes: 20 mg/0.4 mL, 40 mg/0.8 mL)

1. We note that section 16 of the prescribing information details the different needle sizes for each configuration of the prefilled syringes along with the associated NDC. Add the needle size to the “Carton contents” statement. For example:
Carton contents (1 prefilled syringe with (b) (4) gauge needle, 1 package insert...

I. Carton Labeling (Prefilled syringe: 20 mg/0.4 mL carton of 1; 40 mg/0.8 mL carton of 1 and carton of 2)

1. Relocate the medication guide statement (“ATTENTION:Enclosed Medication Guide is required for each patient) to the principal display panel where the statement “Carton (b) (4):...” is located.
2. Relocate the statement “Carton (b) (4):...” to the side panel where the medication guide statement is located.

- J. Carton Labeling (Prefilled syringe: 40 mg/0.8 mL; SureClick autoinjector: 40 mg/0.8 mL)
1. Consider revising the white font used on the side panels to a black font to improve contrast and legibility. As currently presented the small size font and low contrast between the white font over blue background makes the information difficult to read.

Submit revised labeling incorporating the changes shown in the attached marked up labels via email to Sadaf.Nabavian@fda.hhs.gov by COB Wednesday, September 14, 2016, followed by official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/9.7.2016

Cleared by: LJafari/9.9.2016
TBBS/8.24.2016; 9.9.2016

Finalized by: SNabavian/9.9.2016

70 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS)
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/s/

SADAF NABAVIAN
09/09/2016



BLA 761024

GENERAL ADVICE

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your Biologics License Application (BLA) submitted under section 351(k) of the Public Health Service Act for ABP 501.

We also refer to your August 12, 2016, submission, containing your request for review of the proposed suffixes for the nonproprietary name of your product.

We have reviewed your submission and have the following comments:

1. We find your proposed nonproprietary name, adalimumab-atto, unacceptable as the proposed suffix “-atto” includes common medical abbreviations,¹ and may present a risk for errors due to such inclusions.
 - a. ‘att’ is listed as an abbreviation for anti tetanus toxoid
 - b. ‘at’ is listed as an abbreviation for antithrombin
 - c. ‘tt’ is listed as an abbreviation for tetanus toxoid
 - d. ‘to’ is listed as an abbreviation for tincture of opium

2. We find your proposed nonproprietary name, adalimumab (b) (4), unacceptable as the proposed suffix “(b) (4)” includes common medical abbreviations,² and may present a risk for errors due to such inclusions.
 - a. (b) (4)
 - b. (b) (4)
 - c. (b) (4)
 - d. (b) (4)

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

² Neil M Davis, *Medical Abbreviations: 30,000 Conveniences at the Expense of Communication and Safety*. Pennsylvania, 2009

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

3. We find your proposed nonproprietary name, adalimumab-^{(b) (4)} unacceptable as the proposed suffix “^{(b) (4)}” includes common medical abbreviations,³ and may present a risk for errors due to such inclusions.

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

(b) (4)

Additionally, the suffix ‘atto’ returned live trademarks from USPTO. Please ensure that no trademark or other restrictions apply to the proposed suffixes’ that you submit for our evaluation in the context of your nonproprietary name.

To the extent that you have gathered information or data that we might address these concerns and that could support the inclusion of one of these proposed suffixes in your nonproprietary name for ABP 501, we ask that you submit that to us at your earliest convenience. Alternatively, we ask that you submit additional non-meaningful suffixes for our consideration at your earliest convenience.

If you have any questions regarding the contents of this letter or any other aspects of the proper name review process, and would like to schedule a brief teleconference with the Agency, contact Michael Sinks at (240) 402-2684. For any other questions regarding this application, contact Sadaf Nabavian, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2777.

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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/s/

KELLIE A TAYLOR
09/07/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) Biologics License Application (BLA) 761024, submitted on November 25, 2015, is currently under review. We request that you provide your agreement to the postmarketing commitments outlined below, and note that as we continue our review of your 351(k) BLA, additional post-marketing requirements/commitments may be conveyed to you.

1. Perform a drug product shipping study using the approved commercial shipping lane to evaluate the impact of shipment on product quality.

Final Report submission Date: To be provided by Amgen

2. Perform supplemental method validation and introduce a non-reduced CE-SDS test into the integrated control strategy for drug substance manufacture. Submit the analytical procedure, validation report, the proposed acceptance criterion, and the data used to set the acceptance criterion that will be provided in a CBE-0 supplement.

Final Report Submission Date: To be provided by Amgen

Submit your responses via email to Sadaf.Nabavian@fda.hhs.gov by close of business, September 6, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/8.29.2016

Cleared by: LJafari/8.30.2016
TBBS/8.31.2016

Finalized by: SNabavian/8.31.2016

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/s/

SADAF NABAVIAN
08/31/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) Biologics License Application (BLA) 761024, submitted on November 25, 2015, is currently under review. We have the following comments and requests for information.

Please respond to the following comments regarding the hold time validation study which was performed with the process validation lots.

1.



(b) (4)

2.



(b) (4)

Submit your response via email to Sadaf.Nabavian@fda.hhs.gov by Friday, August 26, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Drafted by: NTon/August 24, 2016
Cleared by: LJafari/August 24, 2016
 TBBS/August 24, 2016
Finalized by: NTon/August 24, 2016

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/s/

PHUONG N TON
08/24/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 761024

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Amgen Inc.
One Amgen Center Drive
Mail Stop: 28-2-D
Thousand Oaks, CA 91320

ATTENTION: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs

Dear Mr. Kamassah:

Please refer to your Biologics License Application (BLA) dated and received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP-501, 20 mg/0.4 mL and 40 mg/0.8 mL.

We also refer to your correspondence, dated and received July 14, 2016, requesting review of your proposed proprietary name, Amjevita.

We have completed our review of the proposed proprietary name, Amjevita and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Sadaf Nabavian, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2777.

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/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
08/19/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) Biologics License Application (BLA) 761024, submitted on November 25, 2015, is currently under review. We have the following comments and request for information:

We request the following information to demonstrate your compliance with 21 CFR 820.20 (Management Controls), 21 CFR 820.30 (Design Controls), 21 CFR 820.50 (Purchasing Controls), and 21 CFR 820.100 (CAPA).

1. A description of your firm's organizational structure and how the organizational control is implemented and maintained at all levels.
2. A description of how your firm proposes to control the design of the finished combination product. This would include information pertaining to design planning, design input, design output, design verification, design review, design transfer, design history, and design changes for the proposed finished combination product.
3. A description of your firm's supplier evaluation process and a description of your firm's purchasing controls, including information on how your firm will balance purchasing assessment and receiving acceptance to ensure products and services are acceptable for their intended use.
4. A description of your firm's corrective and preventive action (CAPA) system, including how your CAPA system communicates between the different sites that are involved in the manufacturing of the combination product.
5. A description of the manufacturing process (e.g. diagram) of the overall combination product and the manufacturing controls in place.

Submit your responses via email to Sadaf.Nabavian@fda.hhs.gov by Monday, August 22, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/8.17.2016

Cleared by: LJafari/8.17.2016
TBBS/8.17.2016

Finalized by: SNabavian/8.17.2016

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/s/

SADAF NABAVIAN
08/17/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761024

INFORMATION REQUEST

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your original Biologics License Application received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab).

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 July 21, 2016.

Drug Product: Microbiology

1. The definitive endotoxin test method for drug product release has not been clearly identified. The (b) (4) and kinetic chromogenic test methods have both been qualified for endotoxin release testing of the ABP 501 drug product at AML, and the (b) (4) test method was verified for endotoxin release testing at ADL. To avoid confusion as to which method is the definitive test for the drug product release, the submission should specify only one endotoxin release test method. Please indicate which test method will be used for releasing ABP 501 drug product at these sites and amend section 3.2.P.5 accordingly.
2. The Letter of Authorization (LOA) submitted for Drug Master File (DMF) (b) (4) does not list the (b) (4) components used for the ABP 501 drug product or the relevant (b) (4) sites. Please submit an updated LOA which includes this information and indicates the location of the relevant information within the DMF. In addition, please update section 3.2.P.7 to include the (b) (4) sites for the primary container closure system components that contact the sterile drug product.

Drug Product: Microbiology

3. With reference to the Comparability Protocol submitted for the addition of Amgen Manufacturing Limited building (b) (4) (AML (b) (4) located in Juncos, Puerto Rico, as an alternative ABP, 501 PFS manufacturing facility, please agree to submit the following information in the executed CBE-30.
- a. (b) (4) validation information and data.
 - b. List of other products filled on the same line at AML (b) (4)
 - c. (b) (4) validation data supporting the AML- (b) (4) process. If studies that were performed to validate the (b) (4) process at another site are referenced, explain how these studies support the AML- (b) (4) process (batch size, process parameters, etc.).

If you have any questions, please contact me at 301-796-0962 or 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: 2016.07.01 11:21:40 -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

List of other products filled on the same line at AML (b) (4)

Appears this way on original

If you have any questions, please contact me at 301-796-0962 or keith.olin@fda.hhs.gov.

Senior Project Manager



Keith
Olin

Digitally signed by Keith Olin
Date: 8/12/2016 03:55:19PM
GUID: 5044e4ff00000b14c808af1c62f45a4a



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761024

INFORMATION REQUEST

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your original Biologics License Application received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab).

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 August 17, 2016.

Microbiology:

1. FDA comments on the response dated May 18, 2016 in amendment # 0016:
Please update section 3.2.P.3 and state that the (b) (4) will be used for filling ABP 501 drug product and also provide the list of other products filled on this line.
2. FDA comments on the response dated July 20, 2016 in amendment # 0026:
MET-001000, "Determination of Bacterial Endotoxin Content of Solutions Using Kinetic Limulus Amebocyte Lysate (LAL) Methods", referenced in 3.2.P.5.2 (b) (4)
(b) (4). The scope of this document states that these methods are used for the analysis of the endotoxin samples. It does not specifically state which of these two methods is used for release (b) (4) Please indicate whether (b) (4) (b) (4) will be used for release testing of ABP 501 drug product at AML and ADL sites and amend section 3.2.P.5 accordingly.

Appears this way on original

filing ABP 501 drug product and also provide the list of other products filled on this line.

If you have any questions, please contact me at 301-796-0962 or 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: 2016.08.12 15:53:48 -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

Center for Drug Evaluation and Research



Keith
Olin

Digitally signed by Keith Olin
Date: 8/12/2016 04:12:02PM
GUID: 5044e4ff00000b14c808af1c62f45a4a

Harris, Sarah

From: Kamassah, Augustus <kamassah@amgen.com>
Sent: Thursday, August 04, 2016 3:05 PM
To: Harris, Sarah
Subject: RE: BLA 761024 Nonproprietary Name Teleconference Request

Categories: DPARP

Hello Sarah,

The Amgen team is available to meet with the FDA via teleconference on Wednesday August 10, 2016 from 3:30 - 4:00 PM EST.

The list of Amgen attendees are:

| <u>Name:</u> | <u>Title, Function</u> |
|-------------------------|--|
| Simon Hotchin | Executive Director, Global Biosimilars Regulatory Affairs, CMC |
| Primal Kaur, MD, MBA | Executive Medical Director, Biosimilars Development |
| Augustus Kamassah, MS | Senior Manager, Global Biosimilars Regulatory Affairs |
| Diana Landa, MS | Director, Global Biosimilars Regulatory Affairs |
| Richard Markus, MD, PhD | Vice President, Biosimilars Development |

Call-in Information:

Call-in toll-free number: (b) (4)
Call-in number (b) (4)
Conference Code: (b) (4)

Regards,
Augustus

From: Kamassah, Augustus
Sent: Tuesday, August 02, 2016 5:48 PM
To: Harris, Sarah
Subject: Re: BLA 761024 Nonproprietary Name Teleconference Request

Hello Sarah,

This is to acknowledge receipt of your email. I will follow up with you tomorrow regarding availability of the Amgen team to meet on the 10th of August as proposed by the FDA.

Regards,
Augustus

Sent from my iPhone

On Aug 2, 2016, at 5:31 PM, Harris, Sarah <Sarah.Harris@fda.hhs.gov> wrote:

Good Evening Augustus,

Regarding your submission for BLA 761024, dated and received on July 29, 2016, and your follow up email on August 1, 2016, FDA is requesting a teleconference.

Please confirm your team's availability on Wednesday August 10, 2016 from 3:30 - 4:00 PM EST.

The purpose of the meeting is to discuss a path forward for the nonproprietary name for your pending biosimilar application.

The FDA attendee list is as follows:

Leah Christl, PhD, Associate Director for Therapeutic Biologics, TBBS/OND
Sue Lim, MD, TBBS/OND
Steve Kozlowski, MD, Office of Biotechnology Products
Kellie Taylor, PharmD MPH, Deputy Director, OMEPRM/Office of Surveillance and Epidemiology (OSE)
Jennifer Schwartz, Associate Chief Counsel for Drugs, Office of Chief Counsel (OCC)
Joseph Franklin, Associate Chief Counsel for Drugs, OCC
Patrick Raulerson, Senior Regulatory Counsel, Office of Regulatory Policy (ORP), CDER
Janice Weiner, Senior Regulatory Counsel, ORP, CDER
Sandra Benton, Senior Policy Analyst, Office of Medical Policy
Lubna Merchant, Deputy Director, Division of Medication Errors Prevention and Analysis (DMEPA)
Carlos Mena Grillasca, Safety Evaluator, DMEPA
Bob Ball, Deputy Director, OSE
Yana Mille, RPh, Pharmacologist, Office of Policy for Pharmaceutical Quality, OPQ
Diane Maloney, JD, Associate Director for Policy CBER
Jill Bourdage, RPh, ADRA OSE
Sarah Harris, PharmD, Safety Regulatory Project Manager, OSE
Michael Sinks, PharmD, Safety Regulatory Project Manager, OSE

Please also provide a call-in number and list of Amgen attendees for this meeting.

Kind Regards,
Sarah Harris (on behalf of Mike Sinks)

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

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/s/

SARAH J HARRIS
08/11/2016

**PeRC Meeting Minutes
July 27, 2016**

PeRC Members Attending:

Hari Cheryl Sachs (Acting PeRC Chairperson)

Meshaun Payne

Jackie Yancy

Robert "Skip" Nelson

Barbara Buch

Wiley Chambers

Thomas Smith

Yeruk Mulugeta

Freda Cooner

Gilbert Burkhart

Gerri Baer

Daiva Shetty

Ruthie Davi

Lynne Yao (Non Responsive

Dionna Green

Shrikant Pagay

Greg Reaman

Belinda Hayes

Dianne Murphy

Raquel Tapia

Adrienne Hornatko-Munoz

Agenda

Non Responsive

| | | | | | |
|-------|---------------|---|-------|----------------|---|
| 11:20 | BLA 761024 | Amjevita (Biosimilar to Humira) Full Waiver/Partial Waiver/Deferral/Plan with Agreed iPSP | DPARP | Sadaf Nabavian | Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) in pediatric patients 4 years of age and older, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Adult Ulcerative Colitis (UC) and Plaque Psoriasis (PsO) |
|-------|---------------|---|-------|----------------|---|

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Amjevita (Biosimilar to Humira) Full Waiver/Partial Waiver/Deferral/Plan with Agreed iPSP

- Proposed Indication: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) in pediatric patients 4 years of age and older, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Adult Ulcerative Colitis (UC) and Plaque Psoriasis (PsO)

-  (b) (4)

- *PeRC Recommendations:*

- The PeRC concurred with the plan for a full waiver in pediatric patients for the AS and PSA indications because studies are impossible or highly impractical.
- The PeRC concurred with the plan for a partial waiver for the JIA indication in patients <2 years of age, the CD indication in patients <6 years of age and the UC indication in patients < 5years of age and to the deferral for the JIA indication in patients 2 to <4 years of age, CD in patients 6 to 17 years of age and UC in patients 5 to 17 years of age.
- The PeRC recommended that the waiver for the PsO indication be reconsidered.

 (b) (4)

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Page 8 of 9

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/s/

MESHAUN L PAYNE

08/09/2016



BLA 761024

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

Amgen Inc.
One Amgen Center Drive
Mail Stop: 28-2-D
Thousand Oaks, CA 91320

ATTENTION: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs

Dear Mr. Kamassah:

Please refer to your Biologics License Application (BLA) dated and received November 25, 2016, submitted under section 351(k) of the Public Health Service Act, for Adalimumab ^{(b) (4)}, 20 mg/0.4 mL and 40 mg/0.8 mL.

We acknowledge receipt of your correspondence, dated and received July 14, 2016, requesting a review of your proposed proprietary name, Amjevita.

The user fee goal date is October 12, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Michael Sinks, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-2684. For any other information regarding this application, contact Sadaf Nabavian, Regulatory Project Manager, in the Office of New Drugs at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Dr. Michael Sinks, PharmD
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

MICHAEL A SINKS
08/09/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) Biologics License Application (BLA) 761024, submitted on November 25, 2015, is currently under review. We have the following comments and request for information in response to your June 29, 2016 submission to the BLA titled, "Response to FDA Request for Information dated 7 June 2016."

We generally expect that the release specifications for autoinjectors would include the performance requirements deemed to be essential to the functioning of the device. These may include deliverable volume, injection time and needle extension length. The currently proposed release specifications include deliverable volume and injection time. The June 29, 2016, information amendment references design verification data covered in section 3.2.P.7, which we agree are adequate for the purposes of verifying the design requirements. However, this information is not adequate to assure that the release product meets its performance requirements. Modify the release specifications in Section 3.2.P.5 to include the needle extension length specification, or provide an explanation for how the (b) (4) finished product will meet the needle length extension specification.

Submit your responses via email to Sadaf.Nabavian@fda.hhs.gov by Tuesday, August 2, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/7.28.2016

Cleared by: LJafari/7.29.2016
TBBS/7.29.2016

Finalized by: SNabavian/7.29.2016

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/s/

SADAF NABAVIAN
07/29/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761024

INFORMATION REQUEST

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your original Biologics License Application received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab).

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 August 3, 2016.

3.2.S.4.1 Specification

- 1) We do not agree with your proposal [REDACTED] (b) (4)

[REDACTED]

Please establish release test for [REDACTED] (b) (4) and provide a justification for the proposed acceptance criterion.

3.2.S.5 Reference Standard

- 2) Based on the qualification protocol provided in your IR response dated July 5, 2016 we are unclear if the actual calculated value of potency determined during qualification of reference standards will be reported or if a nominal value of 100% will be used. Please clarify.

3.2.S.7 and 3.2.P.8. Stability

- 3) The quantity of stability data provided is insufficient to justify the proposed shelf life for both Drug Substance and Drug Product in the BLA. Your proposed shelf lives should be revised to the following:
 - a) Revise to (b) (4) months for drug substance.
 - b) Revise to 30 months for the ABP 501 drug product
- 4) The post-approval protocol for DS under accelerated conditions of (b) (4) C should be expanded to include potency (Apoptosis inhibition bioassay) and rCE-SDS.

3.2.P.5.2 Analytical Procedures

- 5) Provide method transfer documents to support the transfer of ABP 501 drug product release methods to Amgen Technology Ireland (ADL).

3.2.R. Drug Product Comparability Protocol

- 6) The comparability protocol proposed for the introduction of AML (b) (4) DP as an alternative DP manufacturing site is insufficient. The assay panel used for the forced degradation assessment in the comparability assessment should be expanded to include all stability indicating assays (i.e., rCE-SDS, potency, CEX-HPLC).

3.2.R Analytical Similarity

- 7) Provide an update on the development of the reverse signaling functional assay. This update should include both any revisions to the proposed timeline provided in the June 27, 2016 IR response and the anticipated number of lots available to be included in the similarity assessment.

Section 3.2.S.2.2 Microbiology Drug Substance

- 8) "Cell culture and Harvest Process Description" indicates that (b) (4)

[Redacted text block]

Please remove the sentence from the BLA.

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Provide both any revisions to the proposed timeline provided in the June 27, 2016 IR response and the anticipated number of lots available to be included in the similarity assessment.

If you have any questions, please contact me at 301-796-0962 or 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,
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Date: 2016.07.27 16:28:40 -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

United States Public Health Service



Keith
Olin

Digitally signed by Keith Olin
Date: 7/27/2016 04:33:22PM
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BLA 761024

GENERAL ADVICE

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your Biologic Licensing Application (BLA) 761024, submitted under section 351(k) of the Public Health Service Act on November 25, 2015.

We also refer to your Proprietary Name Request (PNR) submitted on November 25, 2015 requesting review of your proposed suffixes to be included in your proper name.

FDA requests that Amgen 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 Amgen's proposed biosimilar to Humira 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>).

FDA 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). We note that your November 25, 2015 Proprietary Name Request submission proposes suffixes derived from the Amgen company name. FDA will evaluate these suffixes submitted on November 25, 2015 in parallel to any suffixes you propose that are devoid of meaning.

We encourage Amgen to respond to the information request no later than July 30, 2016. You may include with your submission, or at a later date, any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in the draft guidance. FDA will notify Amgen 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 information regarding this application, contact Sadaf Nabavian, Regulatory Project Manager in the Office of New Drugs, at (301) 796-2777.

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/

KELLIE A TAYLOR
07/18/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your BLA 761024 submitted on November 25, 2015, is currently under review. We are requesting the following information pertaining to the injection depth:

The device release specifications are essential performance characteristics for the needle component which include the characteristics listed below. Provide the following information about the auto-injector:

- Needle injection depth
- Injection initiation at correct needle depth
- Injection completion prior to needle retraction
- Needle fracture / bending stress
- Needle bevel
- Injection pathway patency
- Physical stability of needle / syringe connection

Provide your responses via email to Sadaf.Nabavian@fda.hhs.gov by close of business, Tuesday, July 5, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/6.27.2016
Cleared by: LJafari/6.27.2016
 CDRH/6.28.2016
 TBBS/6.30.2016
Finalized by: SNabavian/6.30.2016

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/s/

SADAF NABAVIAN
06/30/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761024

INFORMATION REQUEST

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your original Biologics License Application received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab).

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 July 5, 2016.

Information Request:

Description of Manufacturing Process and Controls (3.2.S.2.2)

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

Control of Materials (3.2.S.2.3)

4.  (b) (4)

b.

(b) (4)

Elucidation of Structure and Other Characteristics (3.2.S.3.1)

5. Provide information on the batches used to generate characterization data in this section.
6. Provide additional data from the qualification studies or justification to demonstrate that the bioassays for FcγRIIIa binding (158V), ADCC, and CDC used in the analytical similarity assessment are sufficiently sensitive to detect differences in product quality.
7. Provide a summary description of the assay and the source (in-house or commercial) of the antiserum used for detection of host cell protein impurities (HCPs). The anti-HCP antiserum needs to be qualified for its ability to detect potential HCP impurities. (b) (4)

Validation of Analytical Procedure – Identity Test (3.2.S.4.3)

8. One potential identification test for release of both ABP 501 drug substance and ABP 501 drug product is (b) (4). Provide the following information in support of this approach:
 - a. Additional detailed explanation for the how a result of “pass” and “fail” are determined relative to the sample library for (b) (4).
 - b. Specificity data demonstrating that each technique is able to distinguish ABP 501 from other products manufactured in the same facilities.

Drug Substance Specification (3.2.S.4.1)

9. The proposed drug substance specification is inadequate to assure the quality of drug substance. The following additional tests and criteria changes should be implemented:
 - a. A test to assess glycosylation should be established. The proposed acceptance criteria should consider clinical experience and be sufficient to control the effect of glycosylation (e.g., afucosylation, high mannose) on all proposed mechanisms of action.
 - b. Validation batches of ABP 501 DS demonstrate the presence of substantial amounts of residual HCP. A test for HCP should be established for the release of DS.
 - c. Insufficient data are provided to support the claim that charge variants are not considered CQAs. A specification should be established for % acidic peak, % main peak and % basic peak.
 - d. The test of non-reduced CE-SDS should be included as part of the routine release and stability evaluation for drug substance. Alternatively, you should justify the claim that attributes assessed by non-reduced CE-SDS are controlled by orthogonal techniques. This justification should reflect not only levels of total impurities, but also identification of the structure of each individual impurity and its potential for change during shelf life.

BEST AVAILABLE COPY

- e. The acceptance criteria for potency [REDACTED] (b) (4) product quality. Revise the acceptance criteria to be reflective of clinical experience.
- f. A test that evaluates the appearance of the drug substance should be established.

Analytical Methods (3.2.S.4.3)

- 10. Provide additional details to support the transfer of analytical methods from Amgen ATO to Amgen AML. This detail should include qualification protocols and final qualification reports.

Stability (3.2.S.7 and 3.2.P.8)

- 11. The proposed shelf life for Stability period for DS and DP should reflect the quantity of data available from the material in your primary stability program. Provide updated stability data each ongoing stability program including validation batches.
- 12. The BLA includes a commitment to place one Drug Substance batch on a stability protocol under long-term storage condition annually. [REDACTED] (b) (4)
[REDACTED]
[REDACTED]. Incorporate studies with DS held under appropriate accelerated/stressed conditions into the annual stability program.
- 13. The proposed list of tests for the post-approval drug substance stability protocol is not adequate. The protocol should be revised to include tests ongoing in the primary stability program and modifications to the specification resulting from IR item #9.
- 14. The proposed acceptance criteria for the post-approval drug product stability protocol are not adequate. The protocol should be revised to include tests ongoing in proposed in IR item #19.
- 15. Only 16 months of leachables data is available to support the intended drug product shelf life of (b) (4) months. Include a commitment in your stability protocol to assess drug product samples for leachables at the end of shelf. This assessment should also include evaluation any extractables identified in the qualification of your drug substance container closure.

Reference standards (3.2.P.6)

The BLA includes a commitment to place one Drug Substance batch on a stability

- 16. The qualification protocol for establishing new reference standards lacks sufficient control to evaluate the introduction of a new reference standard. The following additional information should be provided:
 - a. Provide the actual qualification protocol.
 - b. Establish criteria to control and evaluate the [REDACTED] (b) (4) of ABP 501. Specific criteria should be proposed for levels of [REDACTED] (b) (4)

The proposed list of tests for the post-approval drug substance stability protocol is

- c. The acceptance criteria for assays that evaluate biological activity (FcRn binding, ADCC, CDC, etc.) should (b) (4) to be reflective of clinical experience.
- d. The tests for potency should be (b) (4) to minimize product drift.

Manufacture (3.2.P.3)

- 17. The process parameters for drug substance (b) (4) should be appropriately validated. The acceptable range as proposed should be revised to include an upper limit or a justification should be provided.

Process Validation (3.2.P.3.5):

- 18. Results demonstrate (b) (4) in both the PFS and AI upon performance of the simulated shipping conditions within the transportation validation study. Provide the following additional information:
 - a. A summary of how the simulated shipping conditions compare to the typical shipping of drug product.
 - b. Any available characterization data, (b) (4)

Drug Product Specification (3.2.P.5.1):

- 19. The proposed drug product specification is inadequate to assure the quality of drug product. The following additional tests and criteria changes should be implemented.
 - a. An individual specification limit should be established for % main peak and % basic peak.
 - b. A test for analysis by non-reduced CE-SDS should be included as part of the routine release and stability test for drug substance. Alternatively, you should justify the claim that attributes assessed by non-reduced CE-SDS are controlled by orthogonal techniques. This justification should reflect not only individual levels of impurities, but also identification of their structure and potential for charge during shelf life.
 - c. The acceptance criteria for potency (b) (4) product quality. Revise the acceptance criteria to be reflective of clinical experience.

Drug Substance Microbiology:

- 20. (b) (4)
- 21. (b) (4)
- 22. (b) (4)
- 23. (b) (4)

If you have any questions, please contact me at 301-796-0962 or keith.olin@fda.hhs.gov.

Sincerely,

Keith J. Olin -S

Digitally signed by Keith J. Olin -S
DN: cn=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: 2016.06.22 19:03:28 -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

Senior Project Manager

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) BLA 761024, submitted on November 25, 2015, is currently under review. We have the following comments and requests for information:

Antibody-mediated reverse signaling is a potential mechanism of action where the antibody cross-links or binds to membrane-bound TNF- α (mTNF) and induces apoptosis or inhibits secretion of pro-inflammatory cytokines. To support your justification for the extrapolation to the Inflammatory Bowel Disease (IBD) indications, compare the ability of ABP-501 and of US-licensed Humira to elicit reverse signaling in your analytical similarity assessment.. Include the following in the study:

1. As a tier 2 attribute, a cell-based assay to evaluate levels of cytokine production and/or apoptosis induction as a result of binding of antibody to mTNF in relevant cells (e.g. Caco-2, Jurkat, or HUVEC). Use a sufficient number of ABP-501 and US-licensed Humira lots to obtain reliable estimates for the mean and variability of both products for quality range testing of the results.
2. As a tier 3 attribute, an evaluation of the affinity of both products to mTNF.

Provide your responses (the study results as part of your analytical similarity assessment) via email to Sadaf.Nabavian@fda.hhs.gov by COB, June 30, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/5.19.2016

Cleared by: TBBS/5.18.2016

JLiu/5.18.2016

MShen/5.19.2016

LJafari/5.19.2016

NNikolov/5.19.2016

Finalized by: SNabavian/5.19.2016

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/s/

SADAF NABAVIAN

05/19/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761024

INFORMATION REQUEST

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your original Biologics License Application received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab).

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 May 19, 2016.

Information Request:**I. Container closure integrity (CCI):**

1. Clarify and confirm that the pre-filled syringe (PFS) units used for qualification of vacuum decay and dye ingress CCI test method are the same as the commercial ABP 501 PFS.
2. Clarify whether the vacuum decay CCI method qualification and testing included positive and negative controls, and provide the following information:
 - a. Describe the preparation of positive control.
 - b. Provide the number of positive and negative controls used for the CCI method qualification and testing.
 - c. Update the method qualification and testing summary results table with the control results.

3. Submit the dye ingress CCI test method qualification report for the ABP 501 syringe primary container system and include the following information: Description of the test including critical parameters (concentration of dye, worst case pressure /vacuum challenge and time of exposure of sample units to the challenge and dye), drug product lots used and the number of positive controls, negative controls and the test units used in the study, preparation of positive and negative controls, and sensitivity of the method (LOD) as a function of breach size. In addition, describe in detail how the LOD of the test was calculated.

II. Drug product manufacturing process

1.

(b) (4)

2.

III. Process Validation

(b) (4)

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

If you have any questions, please contact me at 301-796-0962 or keith.olin@fda.hhs.gov.

Sincerely,

Keith J. Olin -S

Digitally signed by Keith J. Olin -S
DN: cn=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: 2016.05.09 10:01:51 -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 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) BLA 761024, submitted on November 25, 2015, is currently under review. We have the following comments and requests for information:

In study 20120263 we note that there were differences in PASI 75 responders at Week 16 between ABP 501 and EU-approved Humira (see Figure 1), which could be interpreted as clinically meaningful.



We further note that, even though the incidence of the reported neutralizing antibodies (NAb) was similar between ABP 501 and EU-approved Humira, these NABs had an apparent differential effect on efficacy which was more evident in study 20120263 (see Table 1) than in study 20120262 (see Table 2).

We request that you provide your justification of why these differences are not clinically meaningful. This should include patient-level data on the patients who had neutralizing antibodies and where they fell in the spectrum of responses.

In addition, we request that you provide the following information and analyses:

1. Reference is made to section 2.7.2, “Summary of Clinical Pharmacology Studies”.
 - a. Submit the PK analysis datasets and codes/scripts to enable us to recreate Figure 2 and Figure 3 in the “summary of clinical pharmacology studies”. Data files should be submitted as SAS transport files with *.xpt extension (e.g., Data1.xpt) and model code, output listings and scripts used to generate plots should be submitted as ASCII text files with *.txt extension (e.g.:myfile_ctl.txt, myfile_out.txt, myfile_r.txt).

- b. Clarify the “Antidrug Antibody Status” in Figure 3, as to the type of ADA (e.g., binding ADAs or neutralizing ADA), and the time of the ADA status reported (e.g., ADA positive at week 12/16, or ADA positive any time before week 12/16).
2. For each of the comparative clinical studies (20120262 in rheumatoid arthritis and 20120263 in plaque psoriasis), provide a table with the NAb+ patients, their ADA performance at each time point tested, their corresponding PK values, their corresponding PASI scores (for study 20120263) and ACR20 (for study 20120262), and isotype analysis, if available.
3. Provide efficacy analysis for the primary endpoint, % change in PASI, and the secondary endpoints of PASI 75 and sPGA (clear/almost clear) as it relates to subjects who had positive neutralizing antibodies. Consider the following in your analysis:
 - a. From baseline to week 16,
 - b. Post week 16 to the end of the study
 - i. Delineate any subjects with neutralizing antibodies who were not continued on ABP 501 or in the single transition arm because of not meeting the criteria.
4. Provide a discussion of the impact, or lack thereof, of neutralizing antibodies on efficacy for both phases of the study.
5. If there were subjects that used prohibited topical corticosteroids (class I and II), provide an analysis of the distribution of these subjects by arm through week 16. Provide a per protocol analysis through week 16, excluding these subjects.
6. Provide an efficacy analysis [for the primary endpoint, % change in PASI, and the secondary endpoints of PASI 75 and sPGA (clear/almost clear)] through week 16 based on distribution of body weight and baseline disease severity over both arms.
7. Provide an efficacy analysis [for the primary endpoint, % change in PASI, and the secondary endpoints of PASI 75 and sPGA (clear/almost clear)] through week 16 based on subjects with previous anti-TNF exposure.
8. No cases of anaphylaxis have been reported in the clinical studies. Clarify if cases of anaphylaxis have occurred in the ABP 501 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 your responses via email to Sadaf.Nabavian@fda.hhs.gov by COB, Wednesday, May 11, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/5.3.2016

Cleared by: LJafari/5.3.2016

TBBS/5.4.2016

Finalized by: SNabavian/5.4.2016

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/s/

SADAF NABAVIAN
05/04/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) BLA 761024, submitted on November 25, 2015, is currently under review. We have the following request for information:

Submit a review and summary of the available published literature regarding adalimumab use in pregnant and lactating women.

Provide your response via email to Sadaf.Nabavian@fda.hhs.gov by COB, Thursday, April 7, 2016, followed by an official submission to the 351(k) BLA. If there are any questions, contact Sadaf Nabavian, Sr. Regulatory Project Manager, at 301-796-2777.

Drafted by: NTon/March 30, 2016
Cleared by: SBarnes/March 30, 2016
 TBBS/March 30, 2016
Finalized by: NTon/March 30, 2016

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/s/

PHUONG N TON
03/30/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your 351(k) BLA 761024, submitted on November 25, 2015, is currently under review. We have the following comments and requests for information:

- Indicate whether or not auto-injectors (AIs) were used in your PK studies or clinical studies and if there were any failures/malfunctions/medication errors related to the AIs.

Provide your response via email to Sadaf.Nabavian@fda.hhs.gov by COB, Wednesday, March 23, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/3.16.2016
Cleared by: LJafari/3.16.2016
 CDRH/3.16.2016
 TBBS/3.21.2016
Finalized by: SNabavian/3.21.2016

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/s/

SADAF NABAVIAN
03/21/2016

BLA 761024
 ABP 501 (a proposed biosimilar to US-licensed Humira)
 Amgen, Inc.

Dear Mr. Kamassah:

Your BLA 761024 submitted on November 25, 2015, is currently under review. We have the following comments and requests for information:

You have provided data intended to demonstrate your device functionality (such as activation force, needle extension and needle cover override force) is maintained after accelerated aging to simulate (b)(4) years of shelf-life. We are also looking to see if Deliverable Volume/dose accuracy and injection time is also maintained after aging. Provide the location of these data or alternatively submit the data for review.

| Test Name | Acceptance Criteria ^a | Value | T ₀ | T _{0.5} | T ₁ | T ₂ | T ₃ |
|----------------------------------|--|--------------|----------------|------------------|----------------|----------------|----------------|
| Shield Remover Removal Force | (b)(4) kgf | Mean | (b)(4) | (b)(4) | (b)(4) | (b)(4) | (b)(4) |
| | | Max | | | | | |
| | | Min | | | | | |
| | | s | | | | | |
| Needle Cover Pre-Injection Force | (b)(4) kgf | Mean | | | | | |
| | | Max | | | | | |
| | | Min | | | | | |
| | | s | | | | | |
| Activation Force | (b)(4) kgf | Mean | | | | | |
| | | Max | | | | | |
| | | Min | | | | | |
| | | s | | | | | |
| Needle Extension | (b)(4) mm | Mean | | | | | |
| | | Max | | | | | |
| | | Min | | | | | |
| | | s | | | | | |
| Needle cover override force | Max displacement (b)(4) mm with min. applied force of (b)(4) kgf | Mean | | | | | |
| | | Max | | | | | |
| | | Min | | | | | |
| | | s | | | | | |
| Separation Force | ≥ (b)(4) kgf | Average load | | | | | |
| | | Max load | | | | | |
| | | Min load | | | | | |
| | | s | | | | | |

Summarize all of the device-malfunctions, device failures or medication errors/adverse events related to device malfunctions/failures during your bioequivalence or clinical trials. Detail the circumstances of use that resulted in these malfunctions/failures along with the root cause analysis and any mitigation steps that have been consequently instituted.

Provide a response regarding the location of the requested data or provide a projected date to submit the requested information via email to Sadaf.Nabavian@fda.hhs.gov by COB Monday, March 7, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/2.29.2016
Cleared by: LJafari/2.29.2016
 CDRH/3.2.2016
 TBBS/3.3.2016
Finalized by: SNabavian/3.4.2016

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/s/

SADAF NABAVIAN
03/04/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your BLA 761024 submitted on November 25, 2015, is currently under review. We have the following comments and requests for information:

1. Provide the shelf-life of the combination product (ABP 501 filled into the syringe).
2. Indicate whether or not the Deliverable Volume and BLE (break loose extrusion force) tests for the prefilled syringe were conducted right before the stated expiry and whether these same parameters were tested during the shipping study.
3. Provide the shelf-life of the combination product (ABP 501 housed in the autoinjector).

Submit the requested information via email to Sadaf.Nabavian@fda.hhs.gov by COB Monday, March 7, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/3.1.2016
Cleared by: LJafari/3.1.2016
 TBBS/3.2.2016
 CDRH/SShiu/3.4.2016
Finalized by: SNabavian/3.4.2016

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/s/

SADAF NABAVIAN
03/04/2016

BLA 761024
ABP 501 (a proposed biosimilar to US-licensed Humira)
Amgen, Inc.

Dear Mr. Kamassah:

Your BLA 761024 submitted on November 25, 2015, is currently under review. We have the following comments and requests for information:

1. Submit the study subject data listing information below grouped as pdf files, stratified (organized) by clinical study investigator site separately (that is, all requested pdf information for a to f, in one pdf, for each principal investigator site).

Provide the study subject data listings listed below, as applicable for the following Principal Investigators: Dr. Maria Greenwald Site 66011 (Rancho Mirage, CA); Dr. Ramesh Gupta Site 66035 (Memphis, TN), Dr. Piotr Klimiuk Site 48013 (Bialystok, Poland), Dr. Artur Racewicz Site 48001 (Bialystok, Poland), Dr. Jan Brzezicki Site 48003 (Warminsko-Mazurskie, Poland).

- a. Subject discontinuations (If applicable, per treatment group: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation).
- b. Subject assignment per treatment arm (randomization group, if applicable).
- c. Concomitant medication list (non-study medications).
- d. All adverse events (If applicable pretreatment group: preferred term/investigator entry, date start/stopped, severity/resolution, serious adverse event (SAE [yes/no], death [yes/no])).
- e. Primary study efficacy endpoint(s). [Note: Submit the actual raw/unanalyzed data (that is, not derived data or summed subscore or total score e.g., for each patient). For example, provide actual raw score per individual patient per recorded visit for the following: joint swelling or tenderness; actual individual score of the VAS on a 100-mm horizontal VAS; Subject's Investigator's Global Health Assessment (0 to 10); individual HAQ-DI raw score per patient [(dressing, grooming, arising, eating, walking), personal abilities (each patient score for hygiene, reach, grip, activity), use of aids, etc.], or subject's injection site pain perception per patient individual raw score on a 100-mm horizontal VAS.

Additionally, submit documentations (between you as applicant, or your CRO and the clinical study site), if these primary efficacy endpoint raw data from

the clinical study site (source documentation) were re-edited after data lock. Otherwise, submit any relevant documents as deemed necessary.

- f. All major or minor protocol deviation(s) or violation(s).
- 2. Submit all versions and amendments of the informed consent documents (foreign and domestic versions), if not submitted previously under the BLA.

Submit the requested information via email to Sadaf.Nabavian@fda.hhs.gov by COB Thursday, February 11, 2016, followed by an official submission to the BLA. If there are any questions, contact Sadaf Nabavian, Regulatory Project Manager, at 301-796-2777.

Drafted by: SNabavian/2.8.2016
Cleared by: LJafari/2.8.2016
TBBS/2.8.2016
Finalized by: SNabavian/2.8.2016

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/s/

SADAF NABAVIAN
02/08/2016



BLA 761024

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Amgen Inc.
One Amgen Center Drive
Mail Stop 28-2-D
Thousand Oaks, CA 91320-1799

Attention: Augustus Kamassah, MS, RAC
Senior Manager, Global Biosimilars Regulatory Affairs

Dear Mr. Kamassah:

Please refer to your Biologics License Application (BLA) dated November 25, 2015, received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP 501.

ABP 501 is a proposed biosimilar to Humira (adalimumab) (BLA 125057).

We also refer to your amendments dated December 3 and 31, 2015, and January 27, 2016.

We refer to the January 22, 2016, filing notification letter informing you that your 351(k) BLA has been accepted for review with a standard review classification and a September 25, 2016, 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 August 26, 2016.

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

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

1. You have not provided sensitivity analyses that sufficiently evaluate the potential impact of missing data on the reliability of efficacy results in Study 20120262. For the primary endpoint, examine the potential effects of missing data on your results using tipping point sensitivity analyses. These tipping point analyses should include all observed data, including outcomes after patients discontinue study therapy and should vary assumptions about outcomes among the subsets of patients on the ABP 501 arm and the comparator arm who withdrew from the study prior to the planned endpoint. The varying assumptions should include scenarios where dropouts on ABP501 had different future outcomes than dropouts on the comparator arm. The goal is to identify assumptions under which the conclusions change, i.e., under which there is no longer evidence of similarity. Then, the plausibility of those assumptions can be discussed.

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 labeling issue and have the following labeling comments and questions:

1. 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 information to address the above request:

- a. review and summary of the available published literature regarding adalimumab use in pregnant and lactating women.
- b. 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.

2. In the HL Section of the PI, delete the top box that is indicated to the reviewers.
3. In the HL Section of the PI, add the Revision Date.
4. At the bottom of the TOC, delete the last statement.
5. In the FPI, Section 17, Patient Counseling Information, add the following statement:
“Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).”

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 26, 2016. 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.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

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), Medication Guide (MG), and Instructions for Use (IFU). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide (MG), and Instructions for Use (IFU), 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.

The following comments pertain to Polyarticular Juvenile idiopathic Arthritis (pJIA) indication:

We acknowledge receipt of your request for a deferral of the pediatric assessment in patients 2 to < 4 years of age for this application. Once we have reviewed your request, we will notify you if the deferral request is denied.

We acknowledge receipt of your request for a partial waiver of the pediatric assessment in patients age 0 to < 2 years of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

The following comments pertain to Crohn's Disease indication:

We acknowledge receipt of your request for a deferral of the pediatric assessment in patients 6 to 17 years of age for this application. Once we have reviewed your request, we will notify you if the deferral request is denied.

We acknowledge receipt of your request for a partial waiver of the pediatric assessment in patients 0 to < 6 years of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

The following comments pertain to Ulcerative Colitis indication:

We acknowledge receipt of your request for a deferral of the pediatric assessment in patients 5 to 17 years of age for this application. Once we have reviewed your request, we will notify you if the deferral request is denied.

We acknowledge receipt of your request for a partial waiver of the pediatric assessment in patients 0 to < 5 years of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

The following comments pertain to Plaque Psoriasis indication:

We acknowledge receipt of your request for a full waiver of the pediatric assessment 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.

(b) (4)

If you have any questions, call Sadaf Nabavian, Senior Regulatory Project Manager, at (301) 796-2777.

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/

BADRUL A CHOWDHURY
02/05/2016



BLA 761024

FILING NOTIFICATION LETTER

Amgen Inc.
One Amgen Center Drive
Mail Stop 28-2-D
Thousand Oaks, CA 91320-1799

Attention: Augustus Kamassah, MS, RAC
Senior Manager, Global Biosimilars Regulatory Affairs

Dear Mr. Kamassah:

Please refer to your Biologics License Application (BLA) dated November 25, 2015, received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP 501.

ABP 501 is a proposed biosimilar to Humira (adalimumab) (BLA 125057).

We also refer to your amendments dated December 3 and 31, 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 September 25, 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 Sadaf Nabavian, Senior Regulatory Project Manager, at (301) 796-2777.

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/

SARAH K YIM
01/22/2016
Signing for Badrul Chowdhury, M.D., Ph.D.

**MEMORANDUM TO FILE
EXCLUSIVITY EXPIRY UNDER 351(k)(7) of PHS ACT**

To: File for AbbVie Inc.'s BLA 125057 for Humira (adalimumab)

From: The CDER Exclusivity Board

Re: Determination of No Unexpired 351(a) Reference Product Exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Humira (adalimumab) BLA 125057

Date: January 6, 2016

The CDER Exclusivity Board (Board) has determined that there is no unexpired reference product exclusivity under section 351(k)(7) of the Public Health Service (PHS) Act for Humira (adalimumab) (BLA 125057; AbbVie Inc.) that would prohibit the submission, or approval, of any 351(k) application under this statutory provision for a proposed biosimilar (or interchangeable) to Humira (adalimumab).

The reference product exclusivity expiry date is the date on which a 351(k) application referencing the reference product may be licensed assuming it is not blocked by orphan exclusivity, and otherwise meets the requirements for licensure under 351(k). This memorandum does not address orphan exclusivity.

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 125057 for Humira (adalimumab) was first licensed by FDA under section 351(a) of the PHS Act on December 31, 2002. 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 Humira (adalimumab) are December 31, 2006, and December 31, 2014, 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 Humira (adalimumab) under this statutory provision.

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;
Cross-Filed to Amgen's 351(k) application BLA 761024 referencing Humira (adalimumab)

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/s/

MARLENE T SCHULTZ-DEPALO

01/06/2016

Memo entered into DARRTS on behalf of the CDER Exclusivity Board



BLA 761024

INFORMATION REQUEST

Amgen, Inc.
Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Dear Mr. Kamassah:

Please refer to your original Biologics License Application received November 25, 2015, submitted under section 351(k) of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab).

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 January 4, 2016.

1. Please submit the 2016 production schedule for ABP 501 drug substance to be manufactured at Amgen Thousand Oaks (FEI 2026154), and ABP 501 drug product to be manufactured and assembled at Amgen Manufacturing Ltd (FEI 1000110364).
2. For the bioburden and endotoxin tests, provide a description of the test methods and summary qualification data for ABP 501 drug substance (b) (4) samples.

If you have any questions, please contact me at 301-796-0962 or 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: 2015.12.24 12:58:04 -0500

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 761024

BLA ACKNOWLEDGMENT

Amgen
One Amgen Center Drive
Mail Stop 28-2-D
Thousand Oaks, CA 91320-1799

Attention: Augustus Kamassah, MS, RAC
Senior Manager, Global Biosimilars Regulatory Affairs

Dear Mr. Kamassah:

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: "ABP 501", a proposed biosimilar to Humira (adalimumab)

Date of Application: November 25, 2015

Date of Receipt: November 25, 2015

BLA Number: 761024

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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Sadaf Nabavian, Senior Regulatory Project Manager, at (301) 796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, Pharm.D.
Sr. 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/

SADAF NABAVIAN
12/09/2015



IND 111714

MEETING MINUTES

Amgen
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

Attention: Augustus Kamassah, MS
Senior Manager, Global Biosimilars Regulatory Affairs

Dear Mr. Kamassah:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABP 501.

We also refer to the meeting between representatives of your firm and the FDA on June 10, 2015. The purpose of the meeting is to discuss the structure, format, and content of a proposed Biologics License Application (BLA) to be submitted under 351(k) of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab).

A copy of the official minutes of the meeting 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) 796-2777.

Sincerely,
{See appended electronic signature page}

Sadaf Nabavian, PharmD
Sr. 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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 4
Meeting Date and Time: June 10, 2015, from 2:00-3:00 p.m. EST
Meeting Location: WO Building 22, Conference Room 1419
Application Number: IND 111714
Product Name: ABP 501, a proposed biosimilar to US-licensed Humira
Indication: Seeking the same indications for which US-licensed Humira is approved
Sponsor: Amgen
Meeting Chair: Badrul A. Chowdhury, MD, PhD
Meeting Recorder: Sadaf Nabavian, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, M.D., Associate Director, DPARP
Keith Hull, M.D., Ph.D., Clinical Reviewer, DPARP
Nikolay Nikolov, M.D., Clinical Team Leader, DPARP
Carol Galvis, Ph.D., Nonclinical Reviewer, DPARP
Ping Ji, Ph.D., Clinical Pharmacology Reviewer, Office of Translational Sciences (OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology II (DCPII)
Lei He, Ph.D., Clinical Pharmacology Reviewer, OTS, OCP, DCPII
Joel Welch, Ph.D., CMC Team Leader, Office of Pharmaceutical Quality (OPQ), Office of Biotechnology Products (OBP), Division of Biotechnology Review and Research II (DBRRII)
Jun Park, Ph.D., CMC Reviewer, OPQ/OBP/ DBRRII
Juhong Liu, Ph.D., CMC Acting Review Chief, OPQ/OBP/DBRRII
Ruthanna Davi, M.S., Statistical Team Leader, Office of Translational Sciences, (OTS), Office of Biostatistics (OB), Division of Biometrics II (DBVII)
Meiyu Shen, Ph.D., CMC Statistical Reviewer, OTS/OB/DBVI
Gordana Diglisic, M.D., Clinical Team Leader, Division of Dermatology and Dental Products (DDDP)
Kathleen Fritsch, Ph.D., Statistical Reviewer, OTS/OB/DBIII
Daniel Orr, MA, JD, Regulatory Counsel, Office of Regulatory Policy, Division of Regulatory Policy I
Sue Lim, M.D., Senior Staff Fellow, Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Staff (TBBS)
Nicole Verdun, M.D., Clinical Reviewer, OND, TBBS

Anhtu (Annie) Nguyen, RPh, Safety Evaluator, Division of Pharmacovigilance (DPV), Office of Surveillance & Epidemiology (OSE) (on call)

Neil Vora, Pharm.D, MBA, Safety Regulatory Project Manager, OSE

Robert Pratt, PharmD, Office of Surveillance and Epidemiology (OSE), Office of Medication Error Prevention and Risk Management (DMEPA), Division of Risk Management (DRISK) (on call)

Teresa McMillan, PharmD, Safety Evaluator, DMEPA, OSE

Ling-Yu (Eileen) Wu, PhD, DPV, OSE (on call)

Candace Gomez-Broughton, PhD, Microbiology Reviewer, Office of Process and Facilities (OPF), Division of Microbiology Assessment (DMA), Microbiology Assessment Branch IV (MABIV)

Sadaf Nabavian, PharmD, Senior Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Cheryl Anderson, MBA, RAC, Executive Director, Global Biosimilars Regulatory Affairs

Teresa Born, PhD, Director of Research, Biosimilars Development

Richard K Burdick, PhD, Quality Engineer Director

Eric Chi, PhD, Director, Biostatistics, Biosimilars Development

Vincent Fung Sing Chow, PhD, Principal Scientist, Clinical Pharmacology, Modeling, and Simulation

Gay Gauvin, MS, Director, Biosimilars Operations

Kristen Hertwig, MBA, Senior Manager, Global Biosimilars Regulatory Affairs, CMC

Simon Hotchin, Director, Global Biosimilars Regulatory Affairs, CMC

Arunan Kaliyaperumal, PhD, Principal Scientist, Clinical Immunology & Biological Sample Management

Augustus Kamassah, MS, RAC, Senior Manager, Global Biosimilars Regulatory Affairs

Margaret Karow, PhD, Executive Director, Biosimilars Process Development

Primal Kaur, MD, MBA, Executive Medical Director, Biosimilars Development

Diana Landa, MS, Director, Global Biosimilars Regulatory Affairs (on call)

Willy Liou, MS, RAC, Manager, Regulatory Affairs, Devices

Jennifer Liu, PhD, Director, Biosimilars Analytical Sciences

Richard Markus, MD, PhD, Vice President, Biosimilars Development (on call)

Sue Mattheson, Director, Product Quality

Barbara Rellahan, PhD, Director, Product Quality

Nan Zhang, PhD, Senior Manager, Biostatistics, Biosimilars Development

1.0 BACKGROUND

Amgen submitted a BPD Type 4 Meeting Request to discuss the structure, format, and content of a proposed Biologics License Application (BLA) to be submitted under 351(k) of the Public Health Service Act for ABP 501, a proposed biosimilar to US-licensed Humira (adalimumab).

The FDA's preliminary comments were sent to Amgen on June 9, 2015. After review of these comments, Amgen stated their intent to continue with the meeting as scheduled and requested to discuss the FDA's responses to Questions 1, 10, and 13. For the meeting, Amgen provided a

slide presentation, from which some of the information provided in the slides has been incorporated under the Discussion sections under Question 1, 10, and 13. The slides are included in section 6, Attachments and Handouts.

The questions from Amgen are in bold italic, FDA's responses to the questions are in italic, and any discussion that took place between Amgen and the FDA is in regular font.

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 Amgen 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).

2. DISCUSSION

Question 1:

Does the Agency agree with Amgen including information in the prescribing information to identify ABP 501 as a biosimilar to Humira, (b) (4)

FDA Response:

With respect to your draft proposed labeling for ABP 501, it would be reasonable to incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications, as a starting point. Submit your draft proposed labeling for ABP 501 in PLR format. We request that your annotated labeling identify, with adequate specificity, the source of all data and information presented. We will provide additional comments on draft proposed labeling during review of your BLA.

Discussion: (Slide 6)

The Sponsor acknowledged FDA's response and agreed to submit proposed annotated labeling for ABP 501 in PLR format and incorporate the relevant data as recommended by the FDA. The Sponsor stated that they intend to include (b) (4)

The FDA stated that the Sponsor can refer to the approved label for Zarxio as an example, and that the final decision regarding what will be included in the labeling will be a review issue.

Question 2:

Does the FDA agree that Amgen will not be required to include a Risk Evaluation and Mitigation Strategies (REMS) with the BLA?

FDA Response:

In December 2011, FDA released Humira from its previously approved REMS (see December 13, 2011, letter, available at Drugs@FDA). The FDA has also determined that "maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and

significant public health concern and meets the standard in 21 CFR 208.1” (see July 13, 2011, letter, available at Drugs@FDA). Accordingly, at this time, developing a Medication Guide for patients would be appropriate for your proposed biosimilar product.

We intend to make a final determination for the need for a REMS and/or Medication Guide during the review of your application.

Discussion:

No discussion took place.

Question 3:

Since the Humira label has not implemented the new content and format requirements of the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling for human prescription drug and biological products, is it the Agency’s expectation that the draft USPI to be submitted with the BLA will have this new content and format?

FDA Response:

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 and to the Pregnancy and Lactation Labeling (PLLR) final rule (for applications submitted on or after June 30, 2015). 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:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>

Discussion:

No discussion took place.

Question 4:

Does the Agency agree with Amgen’s request to use (b) (4) adalimumab as the proper name for ABP 501?

FDA Response:

At this time, FDA cannot provide additional information regarding the nonproprietary name of your proposed biosimilar product. FDA anticipates that additional information will be provided to you at an appropriate time during the review of your BLA.

Discussion:

No discussion took place.

Question 5:

In order to support effective planning for the review of the BLA, can the Agency provide further details regarding the expected timetable for review, in particular identifying key points at which Agency/Sponsor meetings and inspections will occur?

FDA Response:

At this time, FDA cannot provide additional information regarding the review timelines of meetings or inspections. The general review timelines listed in the briefing package are consistent with the 21st Century good review practice timelines.

Please note that all facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Manufacturing facility information should be included in the 351(k) BLA (3.2.A) as background information for the pre-license inspections.

Discussion:

No discussion took place.

Question 6:

Does the Agency agree that:

a) PK similarity Study 20110217, RA Study 20120262 and Ps Study 20120263 are adequate to support extrapolation to the requested reference product indications?

b) the proposed content of the scientific justification document reflects Agency expectations for reviewing the extrapolation request and that the document to be submitted with the BLA will be adequate to justify extrapolation to each of the indications of use other than RA and Ps?

FDA Response:

If the proposed product meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act based on, among other things, data derived from a clinical study sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, you may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed. However, you would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.

Such scientific justification for extrapolation should address, for example, the following issues for the testing and extrapolating conditions of use:

- *The mechanism(s) of action in each condition of use for which licensure is sought; this may include:*

- *The target/receptor(s) for each relevant activity/function of the product;*
- *The binding, dose/concentration response and pattern of molecular signaling upon engagement of target/receptors;*
- *The relationships between product structure and target/receptor interactions;*
- *The location and expression of the target/receptor(s)*
- *The pharmacokinetics and biodistribution of the product in different patient populations; relevant PD measures also may provide important information on the mechanism of action.*
- *The immunogenicity of the product in different patient populations.*
- *Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to “off-target” activities).*
- *Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population from which licensure is sought.*

Your proposed content of the scientific justification, as outlined in Appendix 4 of the briefing document, appears to reflect our previous discussions and is reasonable. However, the validity of your scientific justification based on the mechanism(s) of action of adalimumab and these additional factors listed above for extrapolating clinical data to indications other than rheumatoid arthritis and plaque psoriasis will be a review issue.

Section 351(k)(2)(A)(i)(II) of the PHS Act requires that a 351(k) application for a proposed biosimilar product include information demonstrating that the proposed biosimilar product and the reference product utilize the same mechanism or mechanisms of action for the condition(s) of use for which licensure is sought, but only to the extent that the mechanism(s) of action are known for the reference product. In FDA’s Guidance for Industry, “Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (2015),” we explain: “If the clinically relevant mechanism(s) of action are known for the reference product or can reasonably be determined, one or more of the functional assays should reflect these mechanisms of action to the extent possible.” Accordingly in your BLA submission, provide functional assays, including mechanism(s) of action, comparing ABP 501 to the reference product (US-licensed Humira) and include a justification that ABP 501 utilizes the same mechanism(s) of action as US-licensed Humira. This data and information should not be limited to the “primary” mechanism of action if other mechanism(s) of action are known or can reasonably be determined. Provide a summary of the data under Module 2.6 (“Nonclinical Written and Tabulated Summaries”) and Module 2.3 (“Quality Overall Summary”) with a link to the relevant section(s) of Module 3.

Discussion:

No discussion took place.

Question 7:

Does the Agency agree with Amgen's plan to locate the extrapolation document in Module 2.5 (Clinical Overview)?

FDA Response:

Your proposal is reasonable.

Discussion:

No discussion took place.

Question 8:

(b) (4)

FDA Response:

We will provide a response to this question in separate correspondence as soon as feasible.

Discussion:

No discussion took place.

Question 9:

Does the Agency agree that the proposed content, structure, and format of the Drug Substance section (3.2.S) will facilitate review of the BLA?

FDA Response:

Your proposed content, structure, and format of the Drug Substance section (3.2.S) appear reasonable.

Discussion:

No discussion took place.

Question 10:

Does the Agency agree that the proposed content, structure, and format of the Drug Product section (3.2.P) will facilitate review of the BLA?

FDA Response:

Your proposed content, structure, and format of the Drug Product section (3.2.P) appear reasonable. However, we note that

(b) (4)

Question 11:

Does the Agency agree that the proposed content, structure, and format of the Appendices section (3.2.A) will facilitate review of the BLA?

FDA Response:

Your proposed content, structure, and format of the Appendices section (3.2.A) appear reasonable.

Discussion:

No discussion took place.

Question 12:

Does the Agency agree that the proposed content, structure, and format of the Regional Information section (3.2.R) will facilitate review of the BLA?

FDA Response:

Your proposed content, structure, and format of the Regional Information section (3.2.R) appear reasonable.

Discussion:

No discussion took place.

Question 13:

Does the Agency agree that, subject to review of the data to be presented in the BLA, the proposed content and presentation of the comprehensive analytical similarity assessment will be sufficient to support a conclusion that:

- ***ABP 501 is analytically similar to the reference product***
- ***and that an acceptable analytical bridge has been established between adalimumab (US) and adalimumab (EU)?***

FDA Response:

Based on the information provided, we cannot agree. We have the following specific concerns:

- *The number of lots you intend to use in the analytical similarity assessment is unclear.*
- *We do not agree with the proposed approach of using (b) (4) criteria for all quality attributes subjected to a statistical analysis. As noted previously, Tier 1 equivalence testing generally would be expected for assay(s) that evaluate clinically relevant quality attributes, such as those related to mechanism(s) of action of the product.*
- *The proposed 3 lots for each product (US-licensed Humira, ABP 501, and EU-approved adalimumab) may not be sufficient to adequately evaluate functional assays.*

Discussion: (Slide 10)

The Sponsor provided clarification on the number of lots that will be used in the analytical similarity assessment, which will consist of up to 10 lots of ABP 501 and 20 lots of US-licensed Humira.

The Sponsor agreed to apply Tier 1 equivalence testing to evaluate clinically relevant quality attributes and those related to the mechanism of action of ABP501. The FDA reiterated that if the Sponsor uses fewer than 10 biosimilar lots for testing, they should consider calculating the confidence interval with a lower confidence level to ensure adequate power. However, the Sponsor would also have to address the issue of a limited number of biosimilar lots with the final manufacturing control strategy.

The Sponsor stated that the biological assays included in Module 3 provide a quantitative comparison of analytical similarity. Additional biological assays will be included in Module 2 and will be considered supportive of the functional similarity of ABP 501 and US-licensed Humira. The FDA asked and the Sponsor agreed to provide justification in the BLA for the selection and the number of lots used in these analyses.

The FDA commented that it will be difficult to do a statistical analysis with only 3 lots. The Sponsor reiterated that some biological assays will be evaluated using Tier 2 testing and not Tier 1 equivalence testing; in those cases, they will justify the number of lots, but the Sponsor stated that 3 lots may be adequate for Tier 2 testing. It was agreed that the number of lots would be a review issue.

The FDA asked when the method qualification reports for assays that support analytical similarity will be available. The Sponsor replied that the reports will be available during inspection. The FDA reminded the Sponsor that the manufacturing schedules should be provided in the 351(k) BLA submission. The Sponsor agreed to provide the manufacturing schedules in the BLA submission.

Post-Meeting Note:

FDA wishes to clarify that attributes evaluated using Tier 1 criteria should include at a minimum potency (apoptosis bioassay), and binding to soluble TNF-alpha.

Question 14:

Does the Agency agree that inclusion of acceptable post-approval change management protocols (PACMPs) [REDACTED] (b) (4) [REDACTED] may be sufficient to result in a reduced reporting category from a post-approval supplement, assuming an acceptable current good manufacturing practices (cGMP) status [REDACTED] (b) (4) at the time of submission?

FDA Response:

Although CFR 601.12(e) and "Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" state that an approved protocol may justify a reduced reporting category for the particular change as defined by a protocol, the appropriateness of a reduced reporting category depends on the scope of the change. At this time, there is insufficient information provided in the meeting background materials for us to assess the scope of the change [REDACTED] (b) (4)

Discussion:

No discussion took place.

Question 15:

Does the Agency agree with Amgen’s proposals regarding the location of the biofunctional characterization data and in vitro pharmacology assessments in Modules 2, 3, and 4 of the BLA?

FDA Response:

We agree with your proposals.

Discussion:

No discussion took place.

Question 16:

Does the FDA agree with the proposed content of the 120-day Safety Update?

FDA Response:

Your proposed content of the 120-day Safety Update is reasonable. We remind you that your application should be complete on submission, meaning that all efficacy and safety data that you consider necessary for approval should be included with the initial submission.

Discussion:

No discussion took place.

Question 17:

Does the Agency agree with Amgen’s plan to summarize the results of the 2 BE studies in Module 2.7.1 and to locate the immunology data from RA Study 20120262 and Ps Study 20120263 in Module 2.7.2, recognizing that the full CSRs will be included in Module 5.3.1.2?

FDA Response:

No, we do not agree. The bioanalytical results of pharmacokinetics and immunogenicity data should be summarized in Module 2.7.1, whereas the summary of pharmacokinetic and immunogenicity data should be located in Module 2.7.2. The analytical validation and study reports for individual study should be in Module 5.3.1.4. The full CSRs and the associated case report forms and data analysis data of human pharmacokinetic and efficacy studies should be placed in Modules 5.3.3 and 5.3.5, respectively.

Discussion:

No discussion took place.

Question 18:

Does the Agency agree that the PK data and analyses described in [Section 7.1](#) are adequate for the BLA to support a demonstration of biosimilarity between ABP 501 and the reference product?

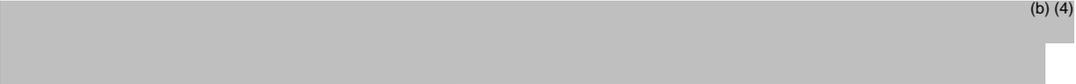
FDA Response:

The proposed approach appears reasonable. The adequacy of the data to support the demonstration of PK similarity between ABP501 and the reference product will be a review issue.

Discussion:

No discussion took place.

Additional Comments:

- I. *The CMC Drug Substance section of the 351(k) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the ABP 501 drug substance. The provided information should include, but not be limited to the following:*
 - a.  (b) (4)
(3.2.S.2.4).
 - b.  (b) (4)
(3.2.S.2.5).
 - c.  (b) (4)
(3.2.S.2.5).
 - d. *Bioburden and endotoxin data obtained during manufacture of at least three process qualification lots (3.2.S.2.5).*
 - e. *Information and summary results from the shipping validation studies (3.2.S.2.5).*
 - f. *Drug substance bioburden and endotoxin release specifications (3.2.S.4).*
 - g.  (b) (4)
(3.2.S.4).
- II. *The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries to support the  processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry “Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products” <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf>.*

Provide information and validation data summaries in Section 3.2.P.3.5 for the following:

- a. [REDACTED] (b) (4).
- b. [REDACTED] (b) (4).
- c. [REDACTED] (b) (4).
- d. [REDACTED] (b) (4).
- e. *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs.*
- f. *A description of the routine environmental monitoring program.*
- g. [REDACTED] (b) (4).
- h. *Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR 610.13(b).*
- i. *Low endotoxin recovery studies. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of endotoxin into undiluted drug product and testing for recoverable endotoxin over time. These studies should be conducted in the containers in which the product and samples are held prior to endotoxin testing.*
- j. *Shipping validation studies.* [REDACTED] (b) (4).
- k. *Container closure integrity testing (3.2.P.2.5). Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress. Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) and at expiry (3.2.P.8.2).*

Additional Discussion:

-The Sponsor had a few follow-up questions with a few updates listed below.

-The Sponsor requested feedback on their request for proprietary name. The FDA responded that a letter will be issued by November time frame.

-Awaiting further guidance from the FDA [REDACTED] (b) (4).

-The Sponsor informed the FDA that an initial pediatric study plan (iPSP) will be submitted to the Division.

-The Sponsor plans to submit the 351(k) application in Q4 of 2014.

Post-Meeting Note:

The FDA confirms the receipt of the iPSP submission and an advice letter will be issued to the Sponsor by August 19, 2015.

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, 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.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms 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](#) 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.*
- *FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.*

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify in a single location, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, BLA 012345, Establishment Information for Form 356h."

| <i>Site Name</i> | <i>Site Address</i> | <i>Federal Establishment Indicator (FEI) or Registration Number (CFN)</i> | <i>Drug Master File Number (if applicable)</i> | <i>Manufacturing Step(s) or Type of Testing [Establishment function]</i> |
|------------------|---------------------|---|--|--|
| 1. | | | | |
| 2. | | | | |

Corresponding names and titles of onsite contact:

| <i>Site Name</i> | <i>Site Address</i> | <i>Onsite Contact (Person, Title)</i> | <i>Phone and Fax number</i> | <i>Email address</i> |
|------------------|---------------------|---------------------------------------|-----------------------------|----------------------|
| 1. | | | | |
| 2. | | | | |

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all clinical studies used to support a demonstration of no clinically meaningful differences between the proposed biosimilar biological product and the reference product in the application. Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

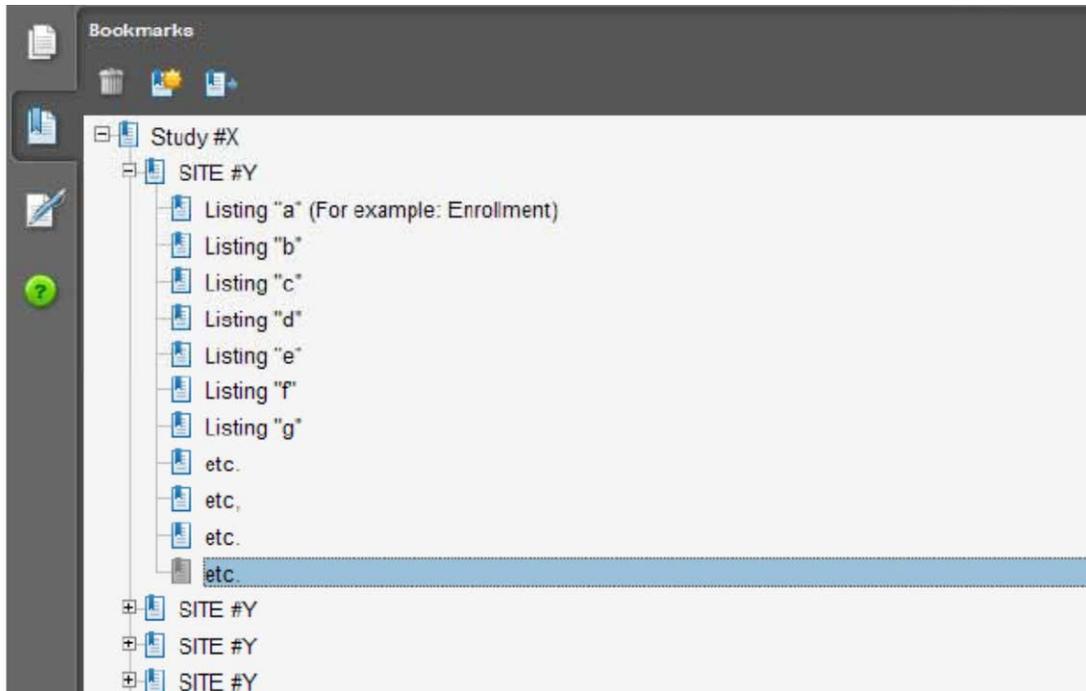
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, by site, in the 351(k) BLA for each of the completed clinical studies:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each clinical study, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each clinical study provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. *For each clinical study: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:*
 - a. *Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated*
 - b. *Subject listing for treatment assignment (randomization)*
 - c. *Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued*
 - d. *Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol*
 - e. *By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)*
 - f. *By subject listing, of AEs, SAEs, deaths and dates*
 - g. *By subject listing of protocol violations and/or deviations reported in the 351(k) BLA, including a description of the deviation/violation*
 - h. *By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.*
 - i. *By subject listing of concomitant medications (as appropriate to the clinical studies)*
 - j. *By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring*
2. *We request that one PDF file be created for each clinical study using the following format:*



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment I

**Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

| DSI Pre-NDA Request Item¹ | STF File Tag | Used For | Allowable File Formats |
|---|-------------------------------------|---|-------------------------------|
| <i>I</i> | <i>data-listing-dataset</i> | <i>Data listings, by study</i> | <i>.pdf</i> |
| <i>I</i> | <i>annotated-crf</i> | <i>Sample annotated case report form, by study</i> | <i>.pdf</i> |
| <i>II</i> | <i>data-listing-dataset</i> | <i>Data listings, by study (Line listings, by site)</i> | <i>.pdf</i> |
| <i>III</i> | <i>data-listing-dataset</i> | <i>Site-level datasets, across studies</i> | <i>.xpt</i> |
| <i>III</i> | <i>data-listing-data-definition</i> | <i>Define file</i> | <i>.pdf</i> |

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

“BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

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

/s/

SADAF NABAVIAN
08/07/2015