

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125504Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)



Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 19 August, 2014
To: Administrative File, STN 125504/0
From: Reyes Candau-Chacon, PhD. Reviewer, OC/OMPQ/DGMPA/BMAB
Through: Patricia Hughes, Ph.D., Team Leader, OC/ OMPQ/DGMPA/BMAB
Subject: New Biologic License Application (BLA)
US License: 1244
Applicant: Novartis Pharmaceuticals Corporation
Facilities: Novartis Pharma S.A.S. Centre de Biotechnologie, 8 rue de l'Industrie, 68330 Huningue, France (FEI 3004864869)
Product: Cosentyx (secukinumab)
Dosage: Sterile lyophilized powder for reconstitution with 1 mL SWFI in 6 mL glass vials containing 150 mg of secukinumab; 150 mg/1 mL solution for injection in a prefilled syringe; 150 mg/1 mL solution for injection in a prefilled syringe assembled into a disposable autoinjector
Indication: For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Due date: October 24, 2014

Recommendation for Approvability: The drug substance part of BLA 125504 is recommended for approval from a microbiology product quality perspective with the following post-marketing commitments:

1. To conduct routine bioburden testing [REDACTED] (b) (4)
[REDACTED] The bioburden method will be qualified with samples from the next production batches in 2015. Routine testing will be implemented for the 2016 manufacturing campaign.
2. To conduct routine bioburden testing [REDACTED] (b) (4)
[REDACTED] The bioburden method will be qualified with samples from the next production batches in 2015. Routine testing will be implemented for the 2016 manufacturing campaign.
3. To conduct routine bioburden and endotoxin testing [REDACTED] (b) (4) Routine testing will be implemented for the 2015 manufacturing campaign.

4. To conduct additional hold time validation studies on two batches at commercial scale (b) (4) validation will be conducted during the 2015 and 2016 commercial campaigns.
5. Evaluate feasibility of (b) (4) secukinumab drug substance and update drug substance specification (b) (4)

Review Summary

Novartis Pharmaceuticals Corporation has submitted BLA 125504 to license secukinumab drug substance and drug product and their manufacturing processes. Secukinumab is a recombinant human IgG1/κ monoclonal antibody against human IL-17 for the treatment of plaque psoriasis. The drug product is supplied as 1 mL sterile solution in a single used pre-filled syringe, a single used autoinjector, and as lyophilized powder for reconstitution in a single used glass vial.

BLA 125504 was submitted in eCTD on October 24, 2013. This review contains the assessment of the manufacturing process of secukinumab bulk drug substance from a microbiological perspective. For review of drug product aspects of the application, please see review by Dr. Kalavati Suvarna.

Amendments Reviewed for Drug Substance Microbial Quality

Information Request date	Question numbers	Amendment sequence	Amendment date
February 22, 2014	1 – 8	0010	March 12, 2014
May 29, 2014	1 – 4	0016	June 11, 2014
June 24, 2014	2d	0020	July 21, 2014

Review Narrative

S DRUG SUBSTANCE

S.1 General Information

Secukinumab (AIN457) is a recombinant human IgG1/κ monoclonal antibody that binds to human IL-17A and neutralizes the bioactivity of this cytokine. Secukinumab is produced in recombinant Chinese Hamster Ovary (CHO) cells and it has (b) (4)

(b) (4)

Satisfactory

S.2 Manufacture

S.2.1 Manufacturer(s)

The following facilities are used for the manufacture, release testing, and stability testing of secukinumab drug substance:

- Novartis Pharma S.A.S. Centre de Biotechnologie, 8 rue de l'Industrie, 68330 Huningue, France; Drug Substance manufacture, release and stability testing except bioassay testing
FEI: 3004864869

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/s/

REYES CANDAU-CHACON
08/20/2014

PATRICIA F HUGHES TROOST
08/20/2014



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Office of Manufacturing and Product Quality
Biotech Manufacturing and Assessment Branch

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

REVIEWER: Kalavati Suvarna, Ph.D.
TEAM LEADER: Patricia Hughes, Ph.D.

BLA	125504/0
APPLICANT	Novartis Pharmaceuticals Corporation
US LICENSE NUMBER	1244
SUBMISSION REVIEWED	Original BLA
PRODUCT	Cosentyx™ (secukinumab, AIN 457, NVP-AIN457-NX-1, AIN457-NXA)
MANUFACTURING FACILITY	Drug Substance: Novartis Pharma S.A.S. Centre de Biotechnologie, 8 rue de l'Industrie, Huningue, France 68330. FEI no: 3007198645 Drug Product: Novartis Pharma Stein AG, Schaffhauserstrasse, Stein, Switzerland 4332. FEI No. 3002653483
INDICATION	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
DOSAGE FORM	Powder for solution, solution for injection (150mg, 150mg/mL)
ROUTE OF ADMINISTRATION	Subcutaneous
SUPPORTING DOCUMENTS	IND100,418, IND113,021, (b) (4), DMF- (b) (4), DMF- (b) (4), DMF- (u) (4), DMF (u) (4), DMF- (u) (4), DMF- (b) (4), Summary of X-Series 510(k)s and Simulated Clinical Use Testing, MAF (b) (4)
CDER RECEIPT DATE	October 24, 2013
REVIEW ASSIGN DATE	October 31, 2013
REVIEW COMPLETE DATE	July 7, 2014
GRMP GOAL DATE	August 31, 2014
PDUFA GOAL DATE	October 24, 2014
PROJECT MANAGER	Mathew White
DIVISION	Division of Dermatology and Dental Products
TO	S:\archive\BLA\125504\STN125504.rev.mem.BLA.07-07-2014.doc

1. PRODUCT QUALITY MICROBIOLOGY SUMMARY

I. EXECUTIVE SUMMARY

The subject of this BLA is COSENTYX™ (secukinumab), a recombinant human IgG1k antibody that binds and neutralizes the proinflammatory cytokine interleukin-17A (IL-17A). The proposed indication for COSENTYX™ is treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Manufacture of secukinumab involves the culture of recombinant Chinese Hamster Ovary (CHO) cells (b)(4)

The final formulation of secukinumab 150 mg Powder for solution for injection consists of 150 mg/mL secukinumab in 30 mM L- histidine (b)(4) pH 5.8, 270 mM sucrose and 0.06% polysorbate 80. The formulation of the liquid drug product for pre-filled syringes consists of 150 mg/mL secukinumab in 20 mM histidine (b)(4) (pH of 5.8 +/- (b)(4)), (b)(4) mM trehalose dihydrate, 5mM L-methionine and 0.02% (w/v) polysorbate 80. Secukinumab is available in three single-use presentations: (a) lyophilisate in vial (150 mg powder for solution for injection) for administration by health care provider, (b) pre-filled syringe (150 mg/1mL), and (c) pre-filled syringe within a SensoReady® pen device (autoinjector) for self-administration. This review covers the assessment of microbial controls of the drug product manufacturing process and sterility assurance of drug product described in the original BLA and amendments (eCTD sequence numbers 0002, 0003, 0004, 0005, 0006, 0012, 0013, and 0017). For a review of the microbial controls in drug substance manufacture, please see the review by Dr. Marie Candauchaon. The drug substance is manufactured at Novartis Pharma S.A.S. Centre de Biotechnologie, 8 rue de l'Industrie, Huningue, France 68330 (FEI no: 3007198645). The drug product is manufactured at Novartis Pharma Stein AG, Schaffhauserstrasse, Stein, Switzerland 4332. FEI No. 3002653483. The drug product manufacturing site in Stein was inspected from March 17-25, 2014 and the inspection has been classified as NAI. The proposed shelf-life for drug product is 24 months at 2-8°C.

II. Recommendation and Conclusion on Approvability

Sections 3.2.P of the BLA pertaining to product quality microbiology aspects of the drug product were reviewed. The BLA, as amended, is recommended for approval from a CMC microbiology product quality perspective. The drug product manufacturing site, Novartis Pharma Stein AG, Schaffhauserstrasse, Stein, Switzerland 4332, was inspected by a team of investigators from March 17-25, 2014 and the inspection was classified as NAI.

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/s/

KALAVATI C SUVARNA
07/17/2014

PATRICIA F HUGHES TROOST
07/17/2014

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: 125504/0 **Applicant:** Novartis Pharmaceuticals Corporation **Stamp Date:** 10/24/2013

Established/Proper Name: Secukinumab **BLA/NDA Type:** Original

On **initial** overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y	
Form 356h completed	Y	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	
Comprehensive Table of Contents	Y	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	
Labeling:	Y	OND and OBP Lead
<input type="checkbox"/> PI –non-annotated	Y	
<input type="checkbox"/> PI –annotated	Y	
<input type="checkbox"/> PI (electronic)	Y	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing	Y N	Not applicable

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	OBP Lead
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	
<input type="checkbox"/> Novel Excipients	N	
<input type="checkbox"/> Executed Batch Records	Y	
<input type="checkbox"/> Method Validation Package	Y	
<input type="checkbox"/> Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		Defer to OBP <div style="background-color: #cccccc; padding: 2px;">(b) (4)</div> testing facility is not indicated Shipping description is incomplete Defer to OBP
<input type="checkbox"/> general info	Y	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> description of manufacturing process and process control	Y	
<input type="checkbox"/> batch numbering and pooling scheme	Y	
<input type="checkbox"/> cell culture and harvest	Y	
<input type="checkbox"/> purification	Y	
<input type="checkbox"/> filling, storage and shipping	Y	
<input type="checkbox"/> control of materials	Y	
<input type="checkbox"/> raw materials and reagents	Y	
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y	
<input type="checkbox"/> justification of specifications		

**PRODUCT QUALITY (Biotechnology)
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CTD Module 3 Contents	Present?	If not, justification, action & status
intermediates		
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y	Initial qualification not included.
<input type="checkbox"/> Filter validation	Y	
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	Y	
<input type="checkbox"/> Validation of aseptic processing (media simulations)	Y	
<input type="checkbox"/> Environmental Monitoring Program	Y	
<input type="checkbox"/> Lyophilizer validation	Y	
<input type="checkbox"/> Other needed validation data (hold times)	Y	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y Y	Manufacturing scale data needs to be requested
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities)	Y	OBP Lead
<input type="checkbox"/> reference standards or materials		Sterility and endotoxin acceptance criteria included
<input type="checkbox"/> container closure system [3.2.P.7]		
<input type="checkbox"/> specifications (vial, elastomer, drawings)		OBP Lead
<input type="checkbox"/> availability of DMF & LOAs	Y	
<input type="checkbox"/> administration device(s)	Y	
<input type="checkbox"/> stability		Consult to CDRH for combination products
<input type="checkbox"/> summary		
<input type="checkbox"/> post-approval protocol and commitment		
<input type="checkbox"/> pre-approval	Y	
<input type="checkbox"/> protocol		OBP Lead
<input type="checkbox"/> results		
<input type="checkbox"/> method validation		
Diluent (vials or filled syringes) [3.2P']		Not applicable
<input type="checkbox"/> description and composition of diluent	Y	
<input type="checkbox"/> pharmaceutical development	Y	
<input type="checkbox"/> preservative effectiveness	Y	
<input type="checkbox"/> container-closure integrity	Y	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	
<input type="checkbox"/> batch formula	Y	

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
<input type="checkbox"/> controls of critical steps and intermediates	Y N	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y N	
<input type="checkbox"/> Filter validation	Y N	
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	Y N	
<input type="checkbox"/> Validation of aseptic processing (media simulations)	Y N	
<input type="checkbox"/> Environmental Monitoring Program	Y N	
<input type="checkbox"/> Lyophilizer sterilization validation	Y N	
<input type="checkbox"/> Other needed validation data (hold times)	Y N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
<input type="checkbox"/> reference standards		
<input type="checkbox"/> container closure system		
<input type="checkbox"/> specifications (vial, elastomer, drawings)	Y N	
<input type="checkbox"/> availability of DMF & LOAs	Y N	
<input type="checkbox"/> stability		
<input type="checkbox"/> summary		
<input type="checkbox"/> post-approval protocol and commitment	Y N	
<input type="checkbox"/> pre-approval		
<input type="checkbox"/> protocol		
<input type="checkbox"/> results		
Other components to be marketed (full description and supporting data, as listed above):		Not applicable. Autoinjector presentation as combination product. There is no separate device.

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
process, from material used in clinical trial to commercial production lots		
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y	OBP Lead
Certification that all facilities are ready for inspection	Y	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	N Y Y Y	Rabbit pyrogen test results for 3 drug product lots to show equivalence were not included. Endotoxin detection is by Kinetic turbidometric method.  (b) (4)
Identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	OBP Lead
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Manufacturing Schedule:

**PRODUCT QUALITY (Biotechnology)
FILING REVIEW FOR ORIGINAL BLA/NDA (OBP & DMPQ)**

1. Please provide the manufacturing schedule for the drug substance and drug product manufacturing sites.

Vial Presentation:

(b) (4)

(b) (4)

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/s/

KALAVATI C SUVARNA
12/03/2013

REYES CANDAU-CHACON
12/03/2013

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12/03/2013