CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125504Orig1s000

CHEMISTRY REVIEW(S)

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: January 23, 2015

Applicant Name: Novartis Pharmaceuticals Corporation
U.S. License #: 1244
STN(s): 125504/0
Product(s): Cosentyx (secukinumab)
Short summary of application: BLA for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

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FACILITY INFORMATION (DRUG SUBSTANCE)

Manufacturing Location: Huningue, France
Firm Name: Novartis Pharma S.A.S. Centre de Biotechnologie
Address: 8 rue de l'Industrie, 68330 Huningue, France
FEI: 3007198645
Short summary of manufacturing activities performed: Drug Substance, release and stability testing except bioassay testing, storage of WCB

Manufacturing Location: Basel, Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35, 4056 Basel, Switzerland
FEI: 3002807772

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[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Short summary of manufacturing activities performed: Bioassay release and stability testing, storage of WCB

Manufacturing Location: (b) (4)
(b) (4)

Short summary of manufacturing activities performed: Bulk harvest viral and mycoplasma testing

Manufacturing Location: (b) (4)
(b) (4)

Short summary of manufacturing activities performed: Bulk harvest viral and mycoplasma testing

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FACILITY INFORMATION (DRUG PRODUCT)

Manufacturing Location: Stein, Switzerland
Firm Name: Novartis Pharma Stein AG
Address: Schaffhauserstrasse, 4332-Stein, Switzerland
FEI: 3002653483
Short summary of manufacturing activities performed: Manufacturing of drug product [lyophilized powder for injection (LYO), pre-filled syringe (PFS), autoinjector assembly (AI)], release and stability testing.

Manufacturing Location: Basel, Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35, CH-4056 Basel, Switzerland
FEI: 3002807772
Short summary of manufacturing activities performed: Bioassay release and stability testing.

Manufacturing Location: (b) (4)
(b) (4)

Short summary of manufacturing activities performed: Break out and sliding force testing at release and stability.

Manufacturing Location: (b) (4)
(b) (4)

Short summary of manufacturing activities performed: Drug product (LYO, PFS, AI) packaging and labeling

Matthew E. White -S

Digitally signed by Matthew E. White -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000479064, cn=Matthew E. White -S
Date: 2014.12.23 10:38:51 -05'00'

Product Quality Review Data Sheet

1. **BLA#** 125504 STN 0

2. **REVIEW#:** 2 (Addendum 1)

3. **REVIEW DATE:** September 19, 2014

4. **REVIEWER(s):** Tura C. Camilli, Ph.D. Tura C. Camilli -A

Sarah B. Kennett, Ph.D. (Team leader) Sarah B. Kennett -S Digitally signed by Sarah B. Kennett -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000597165, cn=Sarah B. Kennett -S Date: 2014.11.03 16:45:41 -05'00'

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS SINCE THE FINALIZATION OF THE INITIAL REVIEW:**

Communication/Document	Date
Information request #6	August 28, 2014
Multi-disciplinary IR	September 26, 2014

6. **SUBMISSION(S) REVIEWED UNDER THIS ADDENDUM:**

Submission	Date Received	Review Completed (Yes/No)
STN 125504/0.30 (response to IR #6)	September 3, 2014	Yes
STN 125504/0.33 (response to Multi-disciplinary IR; PMCs)	October 10, 2014	Yes
STN 125504/0.34 (updates to module 3)	October 17, 2014	Yes

17. ADMINISTRATIVE

Kathleen Clouse, Ph.D., Director, Division of Monoclonal Antibodies

Sarah Kennett, Ph.D., Review Chief, Division of Monoclonal Antibodies

Tura Camilli, Ph.D., Primary Reviewer, Division of Monoclonal Antibodies

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

We recommend approval of the BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of Cosentyx (secukinumab) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by the Agency. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that Cosentyx (secukinumab) be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b) (4) months for secukinumab drug substance when stored at (b) (4)

We recommend an expiration dating period of 36 months for secukinumab drug product (for injection; lyophilized vial) when stored at 2-8°C.

We recommend an expiration dating period of 24 months for secukinumab drug product (injection; pre-filled syringe and autoinjector) when stored at 2-8°C.

II. List Of Deficiencies To Be Communicated

None

III. List Of Post-Marketing Commitments

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

To re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by December 31, 2018.

To re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by December 31, 2019.

To re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by December 31, 2017.

VI. Review of common Technical document-Quality Module 3.2

The initial primary review of module 3.2 is provided in the original review document (August 22, 2014). At the time of the finalization of the primary review, the following CMC issues remained to be addressed:

1) (b) (4)
2) A risk assessment and appropriate extractables and leachables studies for the prefilled syringe container closure.
3) Submission of updated module 3 sections 3.2.S.5 and 3.2.P.3.3 (injection; pre-filled syringe).
4) Dates for fulfillment of the PMCs (refer to PMCs listed above).

Review of these issues and additional information pertaining to these issues received since the time of finalization of the initial primary review is provided below.

1) (b) (4)

2) A request for a risk assessment and any available data from extractables and leachables studies performed for the prefilled syringe was sent to the sponsor on August 28, 2014.

   In the response, the sponsor provided results from an extractables study and an ongoing leachables study. The results of the extractables study using solutions of 95% isoproponal and 0.1% polysorbate 20 indicated that the only extractable present at a relevant level (b) (4) was at a level for which no safety concerns are suggested. The current data (24 months) from an ongoing long term leachable study carried out using representative DP solutions (secukinumab placebo and (b) (4)) stored in the

commercial container closure system under the recommended storage conditions were also provided. The analysis of leachables was performed using GC-MS and LC-UV-MS for the quantification of organic extractables/leachables and IPC/MS for elemental/metal extractables/leachables. The study has not identified the presence of leachables at levels that would represent a safety concern.

Reviewer comment: *Given the issues of using the high concentration DP in the studies, the use of placebo is acceptable. The long term leachable study is ongoing and the sponsor committed to provide data from the 36 month and 48 month time points in the 2015 and 2016 annual reports. This is acceptable.*

3) A request to submit updated module 3 sections 3.2.S.5 and 3.2.P.3 (injection; pre-filled syringe) was made during the late cycle sponsor meeting held on October 8, 2014.

Updated module 3 sections were submitted on October 17, 2014.

Reviewer comment: *The updated sections contain the reference standard information and prefilled syringe identity testing information that was previously included in responses to information requests and deemed acceptable. The information was adequately and accurately updated in the sections provided.*

4) A request for proposed dates for completion of the PMCs was sent to the sponsor on September 26, 2014.

The sponsor provided the dates listed in the PMCs, above.

Reviewer comment: *The dates provided are acceptable.*

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	BLA125504/000	**Action Goal:**	
Stamp Date:	27-JUN-2013	**District Goal:**	24-NOV-2014
Regulatory:	23-JAN-2015		
Applicant:	LEWIS HOWE	**Brand Name:**	COSENTYX
		Estab. Name:	
	, ,	**Generic Name:**	
Priority:	1	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	540	001; INJECTION, SOLUTION; SECUKINUMAB; 150MG 002; INJECTION, POWDER, FOR SOLUTION; SECUKINUMAB; 150MG	

Application Comment: BLA FOR THE TREATMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS IN ADULT PATIENTS WHO ARE CANDIDATES FOR SYSTEMIC THERAPY OR PHOTOTHERAPY (on 25-APR-2014 by T. WILSON () 2404024226)

FDA Contacts:				
	T. CAMILLI	Prod Qual Reviewer		2404029236
	R. CANDAU-CHACON	Micro Reviewer	(HFD-320)	3017960488
	M. WHITE	Regulatory Project Mgr	(HFD-540)	3017964997
	D. KETTL	Team Leader	(HFD-540)	3017962105

Overall Recommendation:	PENDING	on 20-AUG-2014	by EES_PROD
	PENDING	on 25-APR-2014	by EES_PROD

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: (b) (4) TESTING (on 05-SEP-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	05-SEP-2014				WILSONT
OC RECOMMENDATION	17-SEP-2014			ACCEPTABLE	PRABHAKARAR

THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCPETABLE.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** 3004864869

NOVARTIS PHARMA BPO

8 RUE DE l'INDUSTRIE BP 355
HUNINGUE, , FRANCE 68330

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE OTHER TESTER

Establishment Comment: DRUG SUBSTANCE MANUFACTURING, RELEASE AND STABILITY TESTING (EXCEPT BIOASSAY TESTING), STORAGE OF WCB (on 05-SEP-2014 by T. WILSON () 2404024226)

Profile: BIOTECHNOLOGY DERIVED API (STERILE & NON-STERILE) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
INSPECTION PERFORMED	25-MAR-2014		25-MAR-2014		QIUZ
ACCEPTABLE					
SUBMITTED TO OC	25-APR-2014				WILSONT
SUBMITTED TO BMR	20-JUN-2014	Request BMR Evaluation			WILSONT
BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG FROM JANUARY 23 ¿ 31, 2012 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG SUBSTANCE MANUFACTURING AND TESTING OPERATIONS. THE TRP PROFILE WAS UPDATED AND IS ACCEPTABLE. . BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA. PLEASE RESUBMIT THIS TB-EER 15-30 DAYS PRIOR TO THE PLANNED ACTION DATE FOR AN UPDATED COMPLIANCE EVALUATION OF THIS SITE.					
ASSIGNED INSPECTION TO BMR	14-JUL-2014	Product-Specific Inspection			QIUZ
BMAB HAS DETERMINED THIS SITE WILL NEED A PAI					
INSPECTION SCHEDULED	14-JUL-2014		25-MAR-2014		QIUZ
BMR RECOMMENDATION	14-JUL-2014			ACCEPTABLE	QIUZ
NO 483 ISSUED. BMAB FINDS THIS SITE IS ACCEPTABLE FOR THIS BLA.					
SUBMITTED TO DO	14-JUL-2014	10-Day Letter			PRABHAKARAR
BLA PILOT - GMP STATUS IS INITIAL					
DO RECOMMENDATION	01-AUG-2014			ACCEPTABLE	MROSE
OC RECOMMENDATION	04-AUG-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY CDER-OMPQ FROM MARCH 17-25, 2014 AND CLASSIFIED NAI. THIS WAS A PLI COVERING SEKUKINUMAB DRUG SUBSTANCE MANUFACTURING OPERATIONS. THE TRP PROFILE WAS UPDATED AND IS ACCEPTABLE.					

APPEARS THIS WAY ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9692043 **FEI:** 3002653483

NOVARTIS PHARMA STEIN AG

SCHAFFHAUSERSTRASSE 101
STEIN, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

Establishment Comment: MANUFACTURING OF DRUG PRODUCT (LYOPHILIZED POWDER FOR INJECTION PRE-FILLED SYRINGE (PFS), AUTOINJECTOR ASSEMBLY, RELEASE AND STABILITY TESTING (EXCEPT BIOASSAY AND BREAKOUT/SLIDING FORCE TESTING). (on 25-APR-2014 by T. WILSON () 2404024226)

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
INSPECTION PERFORMED	25-MAR-2014		25-MAR-2014		PRABHAKARAR
SUBMITTED TO OC	25-APR-2014				WILSONT
SUBMITTED TO BMR	20-JUN-2014	Request BMR Evaluation			WILSONT
BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG FROM JUNE 11 ¿ 22, 2012 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING STERILE DRUG PRODUCT MANUFACTURING OPERATIONS. THE SVL PROFILE WAS UPDATED AND IS ACCEPTABLE. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA. THIS SITE MAY ALSO REQUIRE A PLI COVERING THE ASSEMBLY PROCESS FOR THE AUTOINJECTOR PEN PRIOR TO APPROVAL OF THIS BLA. BMAB HAS REQUESTED A CDRH CONSULT IN SUPPORT OF MEDICAL DEVICE OPERATIONS FOR THIS COMBINATION DRUG AND DEVICE PRODUCT. PLEASE RESUBMIT THIS TB-EER 15-30 DAYS PRIOR TO THE PLANNED ACTION DATE FOR AN UPDATED COMPLIANCE THIS SITE WAS INSPECTED BY IOG FROM JUNE 11 ¿ 22, 2012 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING STERILE DRUG PRODUCT MANUFACTURING OPERATIONS. THE SVL PROFILE WAS UPDATED AND IS ACCEPTABLE. BMAB (WITH THE INPUT OF OBP) WILL DETERMINE WHETHER THIS SITE REQUIRES A PLI FOR THIS BLA. THIS SITE MAY ALSO REQUIRE A PLI COVERING THE ASSEMBLY PROCESS FOR THE AUTOINJECTOR PEN PRIOR TO APPROVAL OF THIS BLA. BMAB HAS REQUESTED A CDRH CONSULT IN SUPPORT OF MEDICAL DEVICE OPERATIONS FOR THIS COMBINATION DRUG AND DEVICE PRODUCT. PLEASE RESUBMIT THIS TB-EER 15-30 DAYS PRIOR TO THE PLANNED ACTION DATE FOR AN UPDATED COMPLIANCE EVALUATION OF THIS SITE.					
ASSIGNED INSPECTION TO BMR	14-JUL-2014	Product-Specific Inspection			QIUZ
BMAB HAS DETERMINED THIS SITE NEEDS A PAI FOR DP AND DEVICE COVERAGE.					
INSPECTION SCHEDULED	14-JUL-2014		21-MAR-2014		QIUZ
EIR RECEIVED BY OC	11-AUG-2014				PRABHAKARAR
SUBMITTED TO DO FD MFR	17-SEP-2014	10-Day Letter			PRABHAKARAR

APPEARS THIS WAY ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9611204 **FEI:** 3002807772

NOVARTIS RINGASKIDDY PHARMA LTD.

LICHTSRASSE 35
BASEL, , SWITZERLAND

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: DP RELEASE AND STABILITY TESTING (BIOASSAY ONLY); BIOASSAY RELEASE AND STABILITY TESTING, STORAGE OF WCB (on 05-SEP-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	25-APR-2014				WILSONT
OC RECOMMENDATION	20-JUN-2014			ACCEPTABLE	WILSONT
BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG FROM JULY 19 ¿ 26, 2012 AND CLASSIFIED VAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING BIOTECH DRUG TESTING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE. THIS SITE IS SCHEDULED FOR A PLI AND A CGMP SURVEILLANCE INSPECTION ON DECEMBER 2 ¿ 6, 2013. THE FACTS ASSIGNMENT NUMBER FOR THIS INSPECTION IS 8689443. PLEASE RESUBMIT THIS TB-EER 15-30 DAYS PRIOR TO THE PLANNED ACTION DATE FOR AN UPDATED COMPLIANCE EVALUATION OF THIS SITE.					
OC RECOMMENDATION	16-SEP-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY IOG FROM DECEMBER 2-5, 2013 AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION AND A PLI COVERING COSENTYX TESTING (BIOASSAY) OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE LABELER

Establishment Comment: DRUG PRODUCT (LYO, PFS, AI) PACKAGING AND LABELING (on 25-APR-2014 by T. WILSON () 2404024226)

Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	25-APR-2014				WILSONT
OC RECOMMENDATION	20-JUN-2014			ACCEPTABLE	WILSONT
BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY ORA-HQ FROM (b) (4) AND CLASSIFIED VAI. THIS INSPECTION COVERED DRUG PACKAGING AND LABELING OPERATIONS, AND FOUND THE (b) (4) PROFILE (REPACKAGING ONLY) UPDATED AND ACCEPTABLE.					
OC RECOMMENDATION	16-SEP-2014			ACCEPTABLE	PRABHAKARAR
THIS SITE WAS INSPECTED BY (b) (4) FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG PACKAGING AND LABELING OPERATIONS. THE SVL PROFILE (REPACKS ONLY) WAS UPDATED AND IS ACCEPTABLE.					

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: (b) (4) TESTING (on 05-SEP-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	05-SEP-2014				WILSONT
OC RECOMMENDATION	17-SEP-2014			ACCEPTABLE	PRABHAKARAR

THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING STERILE DRUG TESTING OPERATIONS. THE (b) (4) PROFILE WAS UPDATED AND IS ACCEPTABLE. ALTHOUGH THE CTL PROFILE WAS NOT SPECIFICALLY COVERED, THE FACTS ENDORSEMENT TEXT INDICATES THAT THIS INSPECTION PROVIDED GMP COVERAGE OF THE LABORATORY CONTROL SYSTEM.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: DP BREAK OUT AND SLIDING FORCE TESTING. (on 25-APR-2014 by T. WILSON () 2404024226)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment					
OAI Submit To OC					
Request to Extend Re-eval Date To					
Extension Request Comment					
Reason					
SUBMITTED TO OC	25-APR-2014				WILSONT
SUBMITTED TO BMR	20-JUN-2014	Request BMR Evaluation			WILSONT

BLA BACKFILL ONLY - THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTL PROFILE WAS UPDATED AND IS ACCEPTABLE.
THIS SITE MAY REQUIRE A PLI COVERING TESTING OF THE AUTOINJECTOR PEN PRIOR TO APPROVAL OF THIS BLA. BMAB HAS REQUESTED A CDRH CONSULT IN SUPPORT OF MEDICAL DEVICE OPERATIONS FOR THIS COMBINATION DRUG AND DEVICE PRODUCT. PLEASE RESUBMIT THIS TB-EER 15-30 DAYS
PRIOR TO THE PLANNED ACTION DATE FOR AN UPDATED COMPLIANCE EVALUATION OF THIS SITE.

RESUBMISSION FROM BMR	14-JUL-2014	Waive Inspection			QIUZ

NO PAI REQUIRED

OC RECOMMENDATION	17-SEP-2014			ACCEPTABLE	PRABHAKARAR

THIS SITE WAS INSPECTED BY IOG FROM (b) (4) AND CLASSIFIED NAI. THIS WAS A ROUTINE CGMP SURVEILLANCE INSPECTION COVERING DRUG TESTING OPERATIONS. THE CTX PROFILE WAS UPDATED AND IS ACCEPTABLE.

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

/s/

RANJANI PRABHAKARA
09/17/2014

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:
The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS "Communication Group" is "BLA Administrative Form" and the "Communication Name" is "FRM-BLAADMIN-61 – Establishment Evaluation Request Form."

TB-EERs should be submitted:

1) within 10 business days of the application filing date (initial TB-EER)
2) 15-30 days prior to the planned action date (final TB-EER)

When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes. For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: January 23, 2015
Applicant Name: Novartis Pharmaceuticals Corporation
U.S. License #: 1244
STN(s): 125504/0
Product(s): Secukinumab (Cosentyx)

Short summary of application: BLA for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

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FACILITY INFORMATION (DRUG SUBSTANCE)

Manufacturing Location: Huningue, France
Firm Name: Novartis Pharma S.A.S. Centre de Biotechnologie
Address: 8 rue de l'Industrie, 68330 Huningue, France
FEI: 3007198645
Short summary of manufacturing activities performed: Drug Substance, release and stability testing except bioassay testing, storage of WCB

Manufacturing Location: Basel, Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35, 4056 Basel, Switzerland
FEI: 3002807772
Short summary of manufacturing activities performed: Bioassay release and stability testing, storage of WCB

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: (b) (4) testing

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Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: (b) (4) testing

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FACILITY INFORMATION (DRUG PRODUCT)

Manufacturing Location: Stein, Switzerland
Firm Name: Novartis Pharma Stein AG
Address: Schaffhauserstrasse, 4332-Stein, Switzerland
FEI: 3002653483
Short summary of manufacturing activities performed: Manufacturing of drug product [lyophilized powder for injection (LYO), pre-filled syringe (PFS), autoinjector assembly (AI)], release and stability testing.

Manufacturing Location: Basel, Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35, CH-4056 Basel, Switzerland
FEI: 3002807772
Short summary of manufacturing activities performed: Bioassay release and stability testing.

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: Break out and sliding force testing at release and stability.

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: Drug product (LYO, PFS, AI) packaging and labeling

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[3] The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

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/s/

REYES CANDAU-CHACON
09/04/2014

First Approval

Recommendation: Approval

BLA 125504
Review #1
8/28/14

Drug Name/Dosage Form	**Cosentyx (secukinumab)/ for injection (powder); injection (PFS and AI)**
Strength/Potency	**150 mg/ml**
Route of Administration	**Subcutaneous injection**
Rx/OTC Dispensed	**Rx**
Indication	**Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy**
Applicant/Sponsor	**Novartis Pharmaceuticals Corporation**

SUBMISSION(S) REVIEWED	DOCUMENT DATE
STN 125504/0	October 22, 2013
STN 125504/2	December 23, 2013
STN 125504/4	January 15, 2014
STN 125504/7	February 6, 2014
STN 125504/10	March 12, 2104
STN 125504 /11	April 4, 2014
STN 125504/12	April 4, 2014
STN 125504/15	June 11, 2014
STN 125504 /16	June 11, 2014
STN 125504/21	July 23, 2014
STN 125504/23	July 31, 2014
STN 125504/24	August 4, 2014
STN 125504/25	August 8, 2014
STN 125504/27	August 13, 2014
STN 125504/28	August 19, 2014

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	**Tura Camilli**	**OBP/DMA**
Drug Product	**Tura Camilli**	**OBP/DMA**
Immunogenicity	**Tura Camilli**	**OBP/DMA**

Labeling	**Jibril Abdus-Samad**	**OBP**
Facility and Microbiology (DS)	**Maria Caudauchacon**	**DMPQ/BMAB**
Facility and Microbiology (DP)	**Kalavati Suvarna**	**DMPQ/BMAB**
Team Lead	**Sarah Kennett**	**OBP/DMA**
Tertiary Reviewer	**Kathleen Clouse**	**OBP/DMA**

Multidisciplinary Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION
RPM	**Matthew White**	**OND/DDDP**
Cross-disciplinary Team Lead	**David Kettl**	**OND/DDDP**
Medical Officer	**Amy Woitach**	**OND/DDDP**
Pharm/Tox	**Jill Merrill**	**OND/DDDP**
Clinical Pharmacology	**Jie Wang**	**OCP/DCPIII**
Statistics	**Carin Kim**	**OB/DBIII**

Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 351(a)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	Type III		(b) (4)	No review required. Information was in the BLA or previous DMF reviews.
	Type III			No review required. Information was in the BLA or previous DMF reviews.
	Type III			No review required. Information was in the BLA or previous DMF reviews.
	Type III			No review required. Information was in the BLA or previous DMF reviews.
	Type III			No review required. Information was in the BLA or previous DMF reviews.
	Type III			No review required. Information was in the BLA or previous DMF reviews.

B. Other Documents: None

3. CONSULTS:

DISCIPLINE/TOPIC	DATE REQUESTED	STATUS	RECOMMENDATION	REVIEWER
CDRH/ODE/DAGID/ GHDB	11/27/13	Complete	Approvable	Keith Marin
CDRH/OC/DOEA	11/27/13	Complete	Approvable	Viky Verna

Note: Consults were requested by OND.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

a. Recommendation:
The Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125504 for Cosentyx manufactured by Novartis Pharmaceuticals Corporation pending acceptable compliance checks. The data submitted in this application are adequate to support the conclusion that the manufacture of Cosentyx is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

b. Approval action letter language

- Manufacturing location:
  - Drug substance – Novartis Pharma S.A.S. Centre de Biotechnologie, Huningue, France
  - Drug product – Novartis Pharma Stein AG, Stein Switzerland (primary and secondary packaging)

    (b) (4) (secondary packaging)

- Fill size and dosage form:
  - 150 mg/1 ml injection [prefilled syringe (PFS) and autoinjector (AI)] and for injection (lyophilized powder in vial)

- Dating period:
  - Drug product – Lyophilized vial: 36 months; 5 ± 3ºC
    PFS and AI: 24 months; 5 ± 3ºC
  - Drug substance – (b) (4) months; (b) (4) ºC
  - For packaged products: Not packaged
  - Stability option (select one below):
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release
  - Yes
  - Exempt per 21 CFR 601.2a (specified product)

c. Benefit/Risk Considerations:

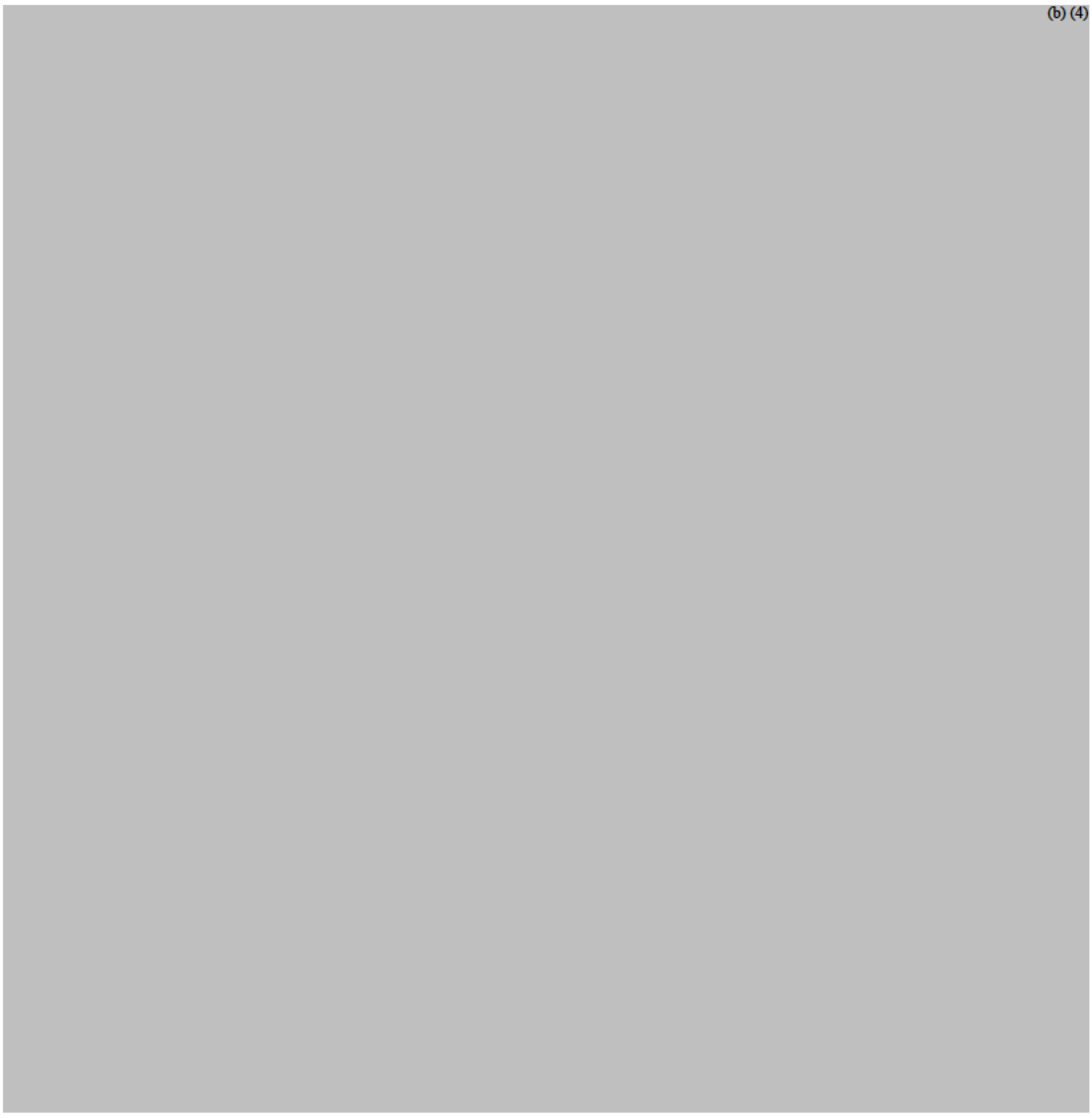
Cosentyx is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

See section B.g., below, for risk considerations related to raw materials. The risk related to use of (b) (4) is currently under discussion within the Office of Biotechnology Products and could lead to an additional PMC, similar to the PMC implemented for a previously approved Novartis BLA.

This BLA initially included little information regarding control of the manufacturing process. For example, non-critical attributes and key operating parameters were not included, it appeared that in-process limits could be changed without notification, development of the drug substance manufacturing process was not described and no data were provided, insufficient validation data were provided, validation protocols for (b) (4) were not included, and insufficient information regarding (b) (4) was provided, which could affect the acceptability of some aspects of the control strategy. In addition, critical quality attributes (CQAs) were not specifically identified. During the review cycle, additional manufacturing process operating ranges and in-process limits were submitted as part of the appropriate sections of the BLA (3.2.S.2.2, 3.2.S.2.4, 3.2.P.3.3, and 3.2.S.P.3.4). The sponsor committed to report changes to limits included in the control of critical steps section. Sufficient information and data regarding th (b) (4) Process validation data were submitted. (b) (4) appropriate concurrent validation protocols for (b) (4) were submitted.

(b) (4)

(b) (4)



B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

To re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXXX, XX, XXXX (Novartis to provide date).

To re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXXX, XX, XXXX (Novartis to provide date).

To re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXXX, XX, XXXX (Novartis to provide date).

II. Summary of Quality Assessments

The sponsor discusses CQAs in general terms and includes the following: degradation products, aggregation products, (b) (4), potency, antibody integrity, and process-related impurities.

A. Active Pharmaceutical Ingredient Intrinsic CQA Identification, Risk and Lifecycle Knowledge Management

The table below provides a summary of product related critical quality attributes and are relevant to both drug substance and drug product. The table includes the identification of the various attributes along with their risk management.

Identification of other CQAs associated with just drug substance (e.g., process related impurities, adventitious agents, pH, appearance, etc.) or drug product are described in separate risk tables in section B, Drug Substance Quality Summary and section C, Drug Product Quality Summary.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA	Risk	Introduction	Control Strategy	Other
(b) (4)				

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/s/

SARAH B KENNETT
08/29/2014

KATHLEEN A CLOUSE STREBEL
08/29/2014

BLA STN 125504

COSENTYX™ (Secukinumab)

Novartis Pharmaceuticals Corporation

Tura Camilli, Ph.D., Reviewer
Sarah Kennett, Ph.D., Review Chief
Division of Monoclonal Antibodies

Product Quality Review Data Sheet

1. BLA# 125504

2. REVIEW DATE: August 18, 2014

3. PRIMARY REVIEW TEAM:

Medical Officer: Amy Woitach and David Kettl (Team leader)
Pharm/Tox: Jill Merrill and Barbara Hill (Team leader)
Product Quality Team: Tura C. Camilli and Sarah Kennett (Team leader)
BMT or Facilities: Maria Caudauchacon, Kalavati Suvarna and Patricia Hughes (Team leader)
Clinical Pharmacology: Jack Wang and Yow Ming Wang (Team leader)
Statistics: Carin Kim and Mohamed Alosh (Team leader)
Pharmacometrics: Jiang Liu and Yaning Wang (Team leader)
Labeling (DMEPA): Carlos Mena Grillasca
DRISK: Robert Pratt and Reema Mehta (Team leader)
OBP Labeling: Jibril Abdus-Samad
CDRH: Keith Marin
RPM: Matthew White

4. MAJOR GRMP DEADLINES

Filing Meeting: December 6, 2014
Mid-Cycle Meeting: June 19, 2014
Wrap-Up Meeting: October 8, 2014
Advisory committee meeting: October 20, 2014
Primary Review Due: August 21, 2014
Secondary Review Due: August 28, 2014
CDTL Memo Due: November 21, 2014
PDUFA Action Date: January 23, 2015

5. COMMUNICATIONS WITH SPONSOR AND OND:

Communication/Document	Date
CMC Pre-BLA Meeting	July 27, 2013
IR in filing letter	December 17, 2013
Information Request #1	March 17, 2014
Information Request #2	May 23, 2014
Information Request #3	July 22, 2014
Information Request #4	August 8, 2014
Information request #5	August 14, 2014
Teleconference	August 18, 2014

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 125504/0	October 22, 2013	Yes
STN 125504/2 (response to BMAB IR)	December 23, 2013	Yes
STN 125504/4 (response to BMAB IR)	January 15, 2014	Yes
STN 125504/7 (response to IR in filing letter)	February 6, 2014	Yes
STN 125504/10 (response to BMAB IR)	March 12, 2104	Yes
STN 125504 /11 (response to IR #1)	April 4, 2014	Yes
STN 125504/12 (response to BMAB IR)	April 4, 2014	Yes
STN 125504/15 (response to BMAB IR)	June 11, 2014	Yes
STN 125504 /16 (response to IR #2)	June 11, 2014	Yes
STN 125504/21 (response to mid-cycle comments)	July 23, 2014	Yes
STN 125504/23 (response to IR #3)	July 31, 2014	Yes
STN 125504/24 (response to IR #3)	August 4, 2014	Yes
STN 125504/25 (response to IR #3)	August 8, 2014	Yes
STN 125504/27 (response to IR #4)	August 13, 2014	Yes
STN 125504/28 (response to IR #5)	August 19, 2014	Yes

7. **DRUG PRODUCT NAME/CODE/TYPE:**

a. Proprietary Name: COSENTYX
b. Trade Name: COSENTYX
c. Non-Proprietary/USAN: secukinumab
d. Chemical name: Recombinant human monoclonal antibody of the IgG1κ (kappa light chain) class to human interleukin-17A (IL-17A)
e. Common name: AIN457
f. INN Name: secukinumab
g. Compendial Name: N/A
h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI_Q16552 (IL 17_AHUMAN) [SECUKINUMAB]
i. Other Names: AIN457, AIN457-NXA, AIN457 Antibody, AIN457 drug substance

8. **PHARMACOLOGIC CATEGORY:** human interleukin17A antagonist

9. **DOSAGE FORM:** Powder for solution for injection (single use vial; lyophilized)
Solution for injection [pre-filled syringe and autoinjector (AI)]

10. **STRENGTH/POTENCY:**

a) The concentration of secukinumab Drug Product is 150 mg/1 ml for all three presentations (after reconstitution of the powder for solution for injection)
b) Potency is defined as percent activity relative to reference standard, using a cell based assay that measures the (b) (4).
c) The potency acceptance criterion is (b) (4)% relative biological activity compared to reference standard.
d) Dating period of DP is 36 months and 24 months for vial and PFS/AI, respectively, when stored at 5°C±3°C.

e) 150 mg secukinumab is filled into 6 ml glass vials or 1ml glass syringes.

11. **ROUTE OF ADMINISTRATION:** subcutaneous injection

12. **RELATED/SUPPORTING DOCUMENTS:**

REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-Reference	COMMENTS (STATUS)
[redacted] (b) (4)			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.
			provided	No review required. Information was in the BLA or previous DMF reviews.

13. **INSPECTIONAL ACTIVITIES**

A pre-approval inspection (PAI) for secukinumab drug substance manufacturing at the Novartis Huningue facility was conducted from March 17 to March 25, 2014 by BMAB reviewer Maria Caudauchacon and DMA reviewers Tura Camilli and Sarah Kennett. The site

is responsible for manufacturing of drug substance and release testing. No 483 observation was issued at the end of the inspection.

A PAI inspection for secukinumab drug product manufacturing at the Novartis Stein facility was conducted from March 17 to March 21, 2014 by BMAB reviewer Kalavati Suvarna and on March 20, 2014 by DMA reviewers Tura Camilli and Sarah Kennett. No 483 observation was issued at the end of the inspection. During the same period, the facility was also inspected by Regina T Brown from OC and a device inspection was carried out by Lt Thomas Peters from ORA.

14. CONSULTS REQUESTED BY OBP

None. OND submitted a consult request to CDRH for the prefilled syringe and autoinjector device constituents of this combination product.

15. QUALITY BY DESIGN ELEMENTS

Risk assessments and design of experiments based studies were used as part of process development.

16. PRECEDENTS

None

17. ADMINISTRATIVE

Kathleen Clouse, Ph.D., Director, Division of Monoclonal Antibodies

Sarah Kennett, Ph.D., Review Chief, Division of Monoclonal Antibodies

Tura Camilli, Ph.D., Primary Reviewer, Division of Monoclonal Antibodies

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

We recommend approval of this BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of Cosentyx (secukinumab) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs. It is recommended that Cosentyx (secukinumab) be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b) (4) months for secukinumab drug substance when stored at (b) (4).

We recommend an expiration dating period of 36 months for secukinumab drug product (for injection; lyophilized vial) when stored at 2-8°C.

We recommend an expiration dating period of 24 months for secukinumab drug product (injection; pre-filled syringe and autoinjector) when stored at 2-8°C.

II. List Of Deficiencies To Be Communicated
None

III. List Of Post-Marketing Commitments
Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

To re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXXX, XX, XXXX (Novartis to provide date).

To re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXXX, XX, XXXX (Novartis to provide date).

To re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided by XXXX, XX, XXXX (Novartis to provide date).

Reviewer comment: [redacted] (b) (4)

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion:
As specified in 21 CFR 25.15(d), Novartis states that this Biologic License Application qualifies for a categorical exclusion to the environmental assessment requirement under 21 CFR 25.31(c), based on consideration of its effects when exposed to the environment. Secukinumab is considered to be a nonhazardous, biodegradable product. The environmental impact in terms of use and disposal is considered to be negligible and, therefore, does not require the preparation of an environmental assessment.

The claim of categorical exclusion is acceptable.

V. Primary Container Labeling Review
CMC review of DP label was generated by Jibril Abdus-Samad, OBP.

VI. Review Of Common Technical Document-Quality Module 3.2
The review of module 3.2 is provided below.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4
A review of the product immunogenicity assays is included at the end of the primary review document

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/s/

TURA C CAMILLI
08/22/2014

LAURIE J GRAHAM on behalf of SARAH B KENNETT
08/22/2014

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

BLA/NDA Number: 125504/0 **Applicant: Novartis** **Stamp Date: October 24, 2013**

Established/Proper Name: secukinumab **BLA/NDA Type: Standard BLA**

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	
❑ 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	
❑ PI –non-annotated	Y	
❑ PI –annotated	Y	
❑ PI (electronic)	Y	
❑ Medication Guide	N	Need to be determined by clinical
❑ Patient Insert	N	Need to be determined by clinical
❑ package and container	Y	
❑ diluent	Y N	Not applicable
❑ other components	Y N	Not applicable
❑ established name (e.g. USAN)	Y	
❑ proprietary name (for review)	Y	

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	
❑ legible	Y	
❑ English (or translated into English)	Y	
❑ compatible file formats	Y	
❑ navigable hyper-links	Y	
❑ interpretable data tabulations (line listings) & graphical displays	Y	
❑ summary reports reference the location of individual data and records	Y	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y	
Companion application received if a shared or divided manufacturing arrangement	Y N	Not applicable

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

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

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	N	Not necessary
Drug Substance [3.2.S]		
❑ general info ○ nomenclature ○ structure (e.g. sequence, glycosylation sites) ○ properties	Y	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	
❑ description of manufacturing process and process control ○ batch numbering and pooling scheme ○ cell culture and harvest ○ purification ○ filling, storage and shipping	Y	
❑ control of materials ○ raw materials and reagents ○ biological source and starting materials ○ cell substrate: source, history, and generation ○ cell banking system, characterization, and testing	Y	
❑ control of critical steps and intermediates ○ justification of specifications ○ stability	Y	
❑ process validation (prospective plan,		

CTD Module 3 Contents	Present?	If not, justification, action & status
results, analysis, and conclusions)	Y	
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y	
❑ characterization of drug substance		
❑ control of drug substance		
○ specifications	Y	
○ ○ justification of specs.	Y	
○ analytical procedures		
○ analytical method validation		
○ batch analyses		
❑ reference standards		
❑ container closure system		
❑ stability	Y	
❑ summary	Y	
❑ post-approval protocol and commitment	Y	
❑ pre-approval		
○ protocol		
○ results		
○ method validation		
Drug Product [3.2.P] [Dosage Form]		
❑ description and composition	Y	
❑ pharmaceutical development	Y	
○ preservative effectiveness	Y N	Not applicable
○ container-closure integrity		
❑ manufacturers (names, locations, and responsibilities of all sites involved)		
❑ batch formula	Y	
❑ 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 Y	
❑ controls of critical steps and intermediates		
❑ process validation including aseptic processing & sterility assurance:	Y	
○ Filter validation		
○ Component, container, closure depyrogenation and sterilization	Y	

CTD Module 3 Contents	Present?	If not, justification, action & status
validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer validation ○ Other needed validation data (hold times) ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin) ❑ control of drug product (justification of specifications; analytical method validation; batch analyses, characterization of impurities) ❑ reference standards or materials ❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ○ administration device(s) ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	Y Y Y Y Y	
Diluent (vials or filled syringes) [3.2P′] ❑ description and composition of diluent ❑ pharmaceutical development ○ preservative effectiveness ○ container-closure integrity ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ 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 Y N Y N Y N Y N	Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance: ○ Filter validation ○ Component, container, closure depyrogenation and sterilization validation ○ Validation of aseptic processing (media simulations) ○ Environmental Monitoring Program ○ Lyophilizer sterilization validation ○ Other needed validation data (hold times) ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards ❑ container closure system ○ specifications (vial, elastomer, drawings) ○ availability of DMF & LOAs ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results	Y N Y N Y N Y N Y N Y N Y N	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y N Y N	Not applicable
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment		

CTD Module 3 Contents	Present?	If not, justification, action & status
○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation, sterilization and storage ○ procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production ❑ novel excipients	Y Y Y N	Not applicable
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	 Y Y Y	
Literature references and copies [3.3]	N	Not necessary (references provided in 3.2)

Examples of Filing Issues	Yes?	If not, justification, action & status
Includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)	Y	
Includes data demonstrating consistency of manufacture	Y	
Includes complete description of product lots and manufacturing process utilized for clinical studies	Y	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y	
Data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
in manufacturing processes or facilities have occurred)		
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: ❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility	N Y Y	Rabbit pyrogen testing on 3 DP lots requested as a review issue.
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	N	Not necessary
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.

- **21 CFR 610.14 states that an identity test must be performed on products after all labeling operations have been completed. Provide information to confirm that identity testing of secukinumab drug product meets this CFR requirement.**

- (b) (4)

- **There are concerns regarding the** (b) (4) .

  1. Provide any available additional data to support (b) (4) **(e.g.,** **additional information and data regarding the** (b) (4) **additional data regarding** (b) (4) **as appropriate).**

  2. If sufficient additional data cannot be supplied at this time, propose additional testing or procedures to confirm th (b) (4) **) using a vial of the MCB and evaluating an appropriate number of** (b) (4)

- **The files in 3.2.A.2.3 cannot be found by our system. Please update the BLA with the correct files. As we cannot open the viral test reports, please confirm that the** (b) (4)

Tura C. Camilli
Product Quality Reviewer(s)

Sarah Kennett
Branch Chief/Team Leader/Supervisor

Kathleen Clouse
Division Director

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/s/

TURA C CAMILLI
12/09/2013

SARAH B KENNETT
12/09/2013

KATHLEEN A CLOUSE STREBEL
12/09/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Instructions:
The review team should upload this form into DARRTS by checking the form in as a communication. The DARRTS "Communication Group" is "BLA Administrative Form" and the "Communication Name" is "FRM-BLAADMIN-61 – Establishment Evaluation Request Form."

TB-EERs should be submitted:

1) within 10 business days of the application filing date (initial TB-EER)
2) 15-30 days prior to the planned action date (final TB-EER)

When requesting establishment evaluations, please include only the site (or sites) directly affected by the proposed changes. For efficacy supplements or license transfers, please include all licensed manufacturing sites.

For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: October 24, 2014

Applicant Name: Novartis Pharmaceuticals Corporation
U.S. License #: 1244
STN(s): 125504/0
Product(s): Secukinumab

Short summary of application: BLA for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

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FACILITY INFORMATION

Manufacturing Location: France
Firm Name: Novartis Pharma S.A.S. Centre de Biotechnologie
Address: 8 rue de l'Industrie, 68330 Huningue, France
FEI: 3007198645
Short summary of manufacturing activities performed: Drug Substance manufacturing, release and stability testing (except bioassay testing)

This site was inspected by IOG from January 23 – 31, 2012 and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug substance manufacturing and testing operations. The TRP profile was updated and is acceptable. . **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.** Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

Manufacturing Location: Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35, 4056
Basel, Switzerland
FEI: 3002807772
Short summary of manufacturing activities performed: Release and stability testing (bioassay only)

This site was inspected by IOG from July 19 – 26, 2012 and classified VAI. This was a routine CGMP surveillance inspection covering biotech drug testing operations. The (b) (4) profile was updated and is acceptable. This site is scheduled for a PLI and a CGMP surveillance inspection on December 2 – 6, 2013. The FACTS assignment number for this inspection is 8689443. Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

Manufacturing Location: Switzerland
Firm Name: Novartis Pharma Stein AG
Address: Schaffhauserstrasse, 4332
Stein, Switzerland
FEI: 3002653483
Short summary of manufacturing activities performed: Manufacturing of drug product (lyophilized powder for injection pre-filled syringe (PFS), autoinjector assembly, release and stability testing (except bioassay and breakout/sliding force testing).

This site was inspected by IOG from June 11 – 22, 2012 and classified VAI. This was a routine CGMP surveillance inspection covering sterile drug product manufacturing operations. The SVL profile was updated and is acceptable. **BMAB (with the input of OBP) will determine whether this site requires a PLI for this BLA.**

This site may also require a PLI covering the assembly process for the autoinjector pen prior to approval of this BLA. BMAB has requested a CDRH consult in support of medical device operations for this combination drug and device product. Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

Manufacturing Location: (b) (4)
Firm Name:
Address:

FEI:
Short summary of manufacturing activities performed: Break out and sliding force testing.

This site was inspected by IOG from [redacted] (b) (4) and classified NAI. This was a routine CGMP surveillance inspection covering drug testing operations. The CTL profile was updated and is acceptable.

This site may require a PLI covering testing of the autoinjector pen prior to approval of this BLA. BMAB has requested a CDRH consult in support of medical device operations for this combination drug and device product. Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation of this site.

Manufacturing Location:
Firm Name:
Address:

[redacted] (b) (4)

FEI:
Short summary of manufacturing activities performed: Drug product (LYO, PFS, AI) packaging and labeling

This site was inspected by ORA-HQ from [redacted] (b) (4) and classified VAI. This inspection covered drug packaging and labeling operations, and found the [redacted] (b) (4) profile (repackaging only) updated and acceptable.

OVERALL RECOMMENDATIONS:

Please resubmit this TB-EER 15-30 days prior to the planned action date for an updated compliance evaluation.

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[3] The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

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/s/

RANJANI PRABHAKARA
12/02/2013

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

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For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date:	October 24, 2014
Applicant Name:	Novartis Pharmaceuticals Corporation
U.S. License #:	1244
STN(s):	125504/0
Product(s):	Secukinumab

Short summary of application: BLA for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

---

FACILITY INFORMATION (DRUG SUBSTANCE)

Manufacturing Location: Huningue, France
Firm Name: Novartis Pharma S.A.S. Centre de Biotechnologie
Address: 8 rue de l'Industrie, 68330 Huningue, France
FEI: 3007198645
Short summary of manufacturing activities performed: Drug Substance, release and stability testing except bioassay testing

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Manufacturing Location: Basel, Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35, 4056 Basel, Switzerland
FEI: 3002807772
Short summary of manufacturing activities performed: Bioassay release and stability testing

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FACILITY INFORMATION (DRUG PRODUCT)

Manufacturing Location: Stein, Switzerland
Firm Name: Novartis Pharma Stein AG
Address: Schaffhauserstrasse, 4332-Stein, Switzerland
FEI: 3002653483
Short summary of manufacturing activities performed: Manufacturing of drug product [lyophilized powder for injection (LYO), pre-filled syringe (PFS), autoinjector assembly (AI)], release and stability testing.

Manufacturing Location: Basel, Switzerland
Firm Name: Novartis Pharma AG
Address: Lichtstrasse 35, CH-4056 Basel, Switzerland
FEI: 3002807772
Short summary of manufacturing activities performed: Bioassay release and stability testing.

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: Break out and sliding force testing at release and stability.

Manufacturing Location: (b) (4)
Firm Name: (b) (4)
Address: (b) (4)
FEI: (b) (4)
Short summary of manufacturing activities performed: Drug product (LYO, PFS, AI) packaging and labeling

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[3] The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

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/s/

KALAVATI C SUVARNA
11/07/2013