

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125504Orig1s000**

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

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
BLA # 125504	NDA Supplement # N/A BLA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Cosentyx Established/Proper Name: Secukinumab Dosage Form: Powder for solution, solution for injection, 150 mg, 150 mg/mL		Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable): N/A
RPM: Matthew White		Division: DDDP
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 type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li><b>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</b></li> <li><b>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</b></li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i>            Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>1/23/15</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions <i>(specify type and date for each action taken)</i></li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

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

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

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

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 |   |

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

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s): Approval 1/21/15
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels ( <b>full color</b> carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name <ul style="list-style-type: none"> <li>Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>Review(s) <i>(indicate date(s))</i></li> </ul>	9/12/13: Proprietary Name Review 9/16/13: Proprietary Name (Cosentyx) Conditionally Accepted 9/16/13: Proprietary Name (Cosentyx Sensoready Pen) Conditionally Accepted 3/20/14: Proprietary name memorandum 5/12/14: Proprietary name conditionally acceptable
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: 12/10/13 DMEPA: 8/28/14 DMPP/PLT (DRISK): 12/10/14 OPDP: 10/14/14 SEALD: CSS: <input checked="" type="checkbox"/> None Other: OBP 12/3/14
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	12/10/13
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input type="checkbox"/> Included N/A
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	

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

<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>7/16/14</u> If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	12/2/13: Acknowledge BLA 12/10/13: Information Request 12/17/13: Filing Communication 1/21/14: Information Request 2/3/14: Review Extension 2/14/14: Information Request 3/4/14: Information Request 3/17/14: Information Request 3/26/14: Information Request 4/10/14: Advice (electronic) 5/22/14: Information Request 5/23/14: Information Request 5/29/14: Information Request 6/18/14: Information Request 6/19/14: Information Request 6/27/14: Information Request 7/22/14: Information Request 8/7/14: Information Request 8/8/14: Information Request 8/14/14: Information Request 8/15/14: Information Request 8/18/14: Advice (verbal) 8/27/14: Information Request 8/28/14: Information Request 9/26/14: Labeling, PMR/PMCs 9/29/14: LCM background pkg. 11/3/14: Labeling comments 11/19/14: Labeling comments 11/26/14: Labeling comments 12/10/14: PMR/PMCs 12/12/14: Information Request 12/22/14: Labeling comments 12/22/14: PMR/PMCs 1/7/15: Labeling comments 1/13/15: Labeling, PMR/PMCs 1/16/15: Labeling, PMR/PMCs
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 7/24/13
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg

• Mid-cycle Communication ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A 6/19/14
• Late-cycle Meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> N/A 10/8/14
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	Guidance: 4/17/13 Guidance: 3/2/11 Guidance: 7/15/09 Guidance: 5/27/09
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	10/20/14
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/20/15
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 1/2/15
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/9/14
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 8
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	12/9/14
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	12/9/14
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None SEALD: 9/8/14 Cardiology: 5/1/14 CBER/DVRPA: 5/13/14 DEPI: 1/20/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" 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 10/7/14
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested OSI Review Summary 8/15/14 Letter-Szepietowski 8/7/14 Letter-Papp 8/18/14

<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/6/13 Filing Review 9/8/14: Discipline Review
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 12/6/13 Filing Review 9/5/14: Discipline Review 12/11/14: Individual Study Summary
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 5/16/14
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 8/7/14
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 8/7/14: Discipline Review 12/2/13 Filing Review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 8/29/14
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/9/14: Discipline Review Addendum 8/7/14: Discipline Review 12/2/13 Filing Review
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input checked="" type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 12/3/13: BMAB Filing Review 7/14/14: BMAB DP Review 7/18/14: Facility Review 7/17/14: DMF Review 8/20/14: BMAB DS Review
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None <b><u>CDRH GHDB</u></b> • 3/13/14: Filing Review • 5/19/14: Consult Review <b><u>CDRH OC:</u></b> • 1/9/14: Consult Review <b><u>CDRH HF:</u></b> 3/24/14: Consult Review
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	8/22/14
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do <b>NOT</b> include EER Detailed Report; date completed must be within <b>2 years</b> of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>5</sup>)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input checked="" type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within <b>30 days</b> of action date) <i>(original and supplemental BLAs)</i>	Date completed: 1/2/15 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i> N/A	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>5</sup> i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • 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> ) N/A
• Finalize 505(b)(2) assessment	<input type="checkbox"/> Done N/A
❖ 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 type="checkbox"/> Done N/A – Application is a BLA
❖ 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/  
-----

MATTHEW E WHITE  
01/23/2015

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:katie.picone@novartis.com)  
**Cc:** [Gould, Barbara](#); [Attinello, Cristina](#); [Phillips, J. Paul \(Paul.Phillips@fda.hhs.gov\)](mailto:Paul.Phillips@fda.hhs.gov)  
**Subject:** BLA 125504 for Cosentyx (secukinumab)  
**Date:** Friday, January 16, 2015 10:50:00 AM

---

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We have reviewed your draft label dated January 15, 2015. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by January 16, 2014.



Agency Proposed  
Label\_1\_16\_15\_BLA :

Please also refer to your proposed postmarketing requirement (PMR) study language dated January 15, 2015. The Agency accepts your proposal to follow each patient in the registry for a minimum of 8 years; however, we require that you submit an interim report after the last patient enrolled in the registry has been followed for a minimum of 5 years. Please submit to your BLA by January 16, 2015 your agreement to conduct the study below and your proposed timeline for protocol submission, interim study report submission, study completion and final report submission.

**PMR Description:** A postmarketing prospective, long-term, observational study to assess the long-term safety of secukinumab compared to other therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy in a real world clinical setting. The study's primary outcome is malignancies. Describe and justify the choice of appropriate comparator population(s). Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate. Specify concise case definitions and validation algorithms for the primary outcome. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment. Provide progress updates on registry patient accrual and demographic summary data in your Annual Report, and provide registry safety data in your Periodic Benefit- Risk Evaluation Reports (PBERs) for the reporting period as well as cumulatively, and a complete final study report.

Protocol Submission: \_\_\_\_\_  
Interim Study Report Submission: \_\_\_\_\_  
Study Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research Food  
and Drug Administration

**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
01/16/2015

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:katie.picone@novartis.com)  
**Cc:** [Gould, Barbara](#); [Attinello, Cristina](#)  
**Subject:** BLA 125504 for Cosentyx (secukinumab): Agency proposed label and revised PMR  
**Date:** Tuesday, January 13, 2015 5:13:00 PM  
**Attachments:** [Agency Proposed Label 1\\_13\\_15\\_BLA 125504\\_Cosentyx.doc](#)

---

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We have reviewed your draft label dated January 8, 2015. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by January 15, 2014.



Agency Proposed  
Label\_1\_13\_15\_BLA :

Please also refer to the postmarketing requirement (PMR) study sent by the Agency via email on December 22, 2014 and your subsequent response dated December 23, 2014. The Agency has the following revisions to this PMR study

**PMR Description:** A postmarketing prospective, long-term, observational study to assess the long-term safety of secukinumab compared to other therapies used in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy in a real world clinical setting. The study's primary outcome is malignancies. Describe and justify the choice of appropriate comparator population(s). Design the study around a testable hypothesis to assess, with sufficient sample size and power, a clinically meaningful increase in malignancy risk above the comparator background rate. Specify concise case definitions and validation algorithms for the primary outcome. Enroll patients over an initial 4-year period and follow for a minimum of <sup>(b) (4)</sup> years from the time of enrollment. Provide progress updates on registry patient accrual and demographic summary data in your Annual Report, and provide registry safety data in your Periodic Benefit-Risk Evaluation Reports (PBERs) for the reporting period as well as cumulatively, and a complete final study report.

Protocol Submission: \_\_\_\_\_

Study Completion: \_\_\_\_\_

Final Report Submission: \_\_\_\_\_

Please submit to your BLA by January 15, 2015 your agreement to conduct the study above and your timeline for protocol submission, study completion, and final report submission.

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
01/13/2015

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:katie.picone@novartis.com)  
**Cc:** [Phillips, J. Paul \(Paul.Phillips@fda.hhs.gov\)](mailto:Paul.Phillips@fda.hhs.gov); [Gould, Barbara](#)  
**Subject:** BLA 125504 for Cosentyx (secukinumab): Agency Proposed Label  
**Date:** Wednesday, January 07, 2015 3:05:00 PM

---

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We have reviewed your draft label dated December 23, 2014. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by January 9, 2014.



Agency Proposed  
Label\_1\_7\_15\_BLA 1

Regards,

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research Food  
and Drug Administration

**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
01/07/2015

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:Katie.picone@novartis.com)  
**Cc:** [Gould, Barbara](mailto:Barbara.Gould@fda.hhs.gov); [Phillips, J. Paul \(Paul.Phillips@fda.hhs.gov\)](mailto:Paul.Phillips@fda.hhs.gov)  
**Subject:** BLA 125504 for Cosentyx (secukinumab): PMR  
**Date:** Monday, December 22, 2014 1:56:00 PM

---

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

The Agency has identified the following additional postmarketing requirement (PMR) to be conducted post approval.

PMR Description: Enroll 4000 Cosentyx-treated patients into a registry and follow up for 5 years from the time of enrollment to assess the incidence and nature of malignancies.

Final Protocol Submission:	_____
Study Completion:	_____
Final Report Submission:	_____

Please submit to your BLA by December 29, 2014 your agreement to conduct the study above and your timeline for final protocol submission, study completion, and final report submission.

Regards,

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
12/22/2014

**From:** White, Matthew  
**To:** Picone, Katie ([katie.picone@novartis.com](mailto:katie.picone@novartis.com))  
**Cc:** Gould, Barbara; Phillips, J. Paul ([Paul.Phillips@fda.hhs.gov](mailto:Paul.Phillips@fda.hhs.gov))  
**Subject:** BLA 125504 for Cosentyx (secukinumab): Agency Proposed Label  
**Date:** Friday, December 19, 2014 5:16:00 PM

---

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We have reviewed your draft label dated December 4 and 17, 2014. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by December 24, 2014.



Agency Proposed  
PI\_12\_19\_14\_BLA 12



Agency Proposed  
Medication Guide\_12\_



Agency Proposed  
IFU\_Sensoready Pen



Agency Proposed  
IFU\_PFS\_12\_19\_14\_



Agency Proposed  
IFU\_Vial\_12\_19\_14\_

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)  
**Phone:** 301-796-4997  
**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
12/22/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Director, Drug Regulatory Affairs  
One Health Plaza  
Building 135, Office 414  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to your December 4, 2014 submission, containing revised labeling and your rationale for the proposed changes.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response by December 17, 2014.

In your 12/4/2014 submission, you state the needle caps contain (b) (4) natural rubber latex, and you adjusted your labeling in the Package Insert (PI), Medication Guide (MG), and prefilled-syringe Instructions for Use (IFU) accordingly. However, based on the FDA guidance for industry *User Labeling for Devices that Contain Natural Rubber* (21 CFR 801.437) (b) (4)

Ensure you are interpreting the Guidance correctly.

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070929.pdf>

The following actions are needed pending your confirmation of the correct rubber nomenclature:

Natural Rubber Latex

- Revise all rubber statements in the PI, MG, and IFUs for consistency

- Revise all Carton Labeling rubber statements from “(b) (4)” to “Caution: Contains Natural Rubber Latex Which May Cause Allergic Reaction” and submit to the BLA.

(b) (4)

- Revise all rubber statements in the PI, MG, and IFUs for consistency. Note, the Carton Labeling already states “(b) (4)”.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

Kendall A. Marcus, MD  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

JILL A LINDSTROM

12/12/2014

signed on behalf of Dr. Kendall Marcus

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:Katie.picone@novartis.com)  
**Cc:** [Gould, Barbara](mailto:Paul.Phillips@fda.hhs.gov); [Phillips, J. Paul \(Paul.Phillips@fda.hhs.gov\)](mailto:Paul.Phillips@fda.hhs.gov)  
**Subject:** BLA 125504 for Cosentyx (secukinumab): PMRs/PMCs  
**Date:** Wednesday, December 10, 2014 3:54:00 PM

---

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

The Agency has identified the following additional postmarketing requirements (PMRs)/postmarketing commitments (PMCs) to be conducted post approval. Please note that additional PMRs/PMCs may be forthcoming.

**PMR:**

**PMR Description:** Complete the treatment and evaluation of subjects enrolled in the ongoing CAIN457A2302E1 and CAIN457A2304E1 trials for a duration of at least 4 years unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through the end of the trial (even if treatment is not continued for the duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events.

Final Protocol Submission: \_\_\_\_\_

Trial Completion: \_\_\_\_\_

Final Report Submission: \_\_\_\_\_

**PMC:**

**PMC Description:** Conduct a clinical trial to evaluate the treatment effect and safety profile of a higher dose (e.g., 450 mg) of secukinumab in psoriasis subjects with higher body weight and to explore the option of dose escalation to 450 mg for those who cannot achieve the therapeutic goal at 300 mg dose.

Final Protocol Submission: \_\_\_\_\_

Trial Completion: \_\_\_\_\_

Final Report Submission: \_\_\_\_\_

Please submit to your BLA by December 15, 2014 your agreement to conduct the studies above and your timeline for final protocol submission, study completion, and

final report submission for each PMR/PMC.

Regards,

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
12/10/2014

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:katie.picone@novartis.com)  
**Cc:** [Gould, Barbara](#)  
**Subject:** BLA 125504 for Cosentyx (secukinumab): Agency Proposed PI  
**Date:** Wednesday, November 26, 2014 9:36:00 AM

---

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We have reviewed your draft package insert (PI) dated October 10, 2014. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by December 8, 2014.



Agency Proposed  
PI\_11\_26\_14\_BLA 12

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research Food  
and Drug Administration

**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
11/26/2014

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:Katie.Picone@Novartis.com)  
**Cc:** [Gould, Barbara](#)  
**Subject:** BLA 125504 for Cosentyx (secukinumab): Carton/container labeling  
**Date:** Wednesday, November 19, 2014 10:36:00 AM  
**Attachments:** [image001.png](#)

---

Dr. Picone,

In regards to BLA 125504 for Cosentyx (secukinumab), please refer to your November 10, 2014 submission containing revised carton and container labeling.

The carton labeling for the prefilled syringes and Sensoready Pens (pack of 2) now include the statement "CONTAINS TWO UNITS THAT MAY NOT BE SOLD SEPARATELY". We do not object to these statements as they do not crowd the labels and would prevent unintended practices. However, you submitted a new Sensoready Pen label (see below) with the added statement (b) (4). We object to the use of this statement as it is ambiguous and unnecessary (i.e., the carton already states that the 2 units may not be sold separately).



Please resubmit draft carton and container labeling with our comments addressed or your counterproposal by November 26, 2014.

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)  
**Phone:** 301-796-4997  
**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
11/19/2014

**From:** White, Matthew  
**To:** Picone, Katie ([katie.picone@novartis.com](mailto:katie.picone@novartis.com))  
**Cc:** Gould, Barbara  
**Subject:** BLA 125504 for Cosentyx (secukinumab): Carton/Container Labeling  
**Date:** Monday, November 03, 2014 4:33:00 PM  
**Attachments:** [BLA 125504\\_Cosentyx\\_Agency Carton\\_Container Comments\\_11\\_3\\_14.doc](#)

---

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We have reviewed the draft carton and container labeling received October 10, 2014 and our comments are attached. Please resubmit draft carton and container labeling with our comments addressed or your counterproposal by November 10, 2014.



BLA  
125504\_Cosentyx\_Ag

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
11/03/2014

---

**From:** Phillips, J. Paul  
**Sent:** Friday, September 26, 2014 2:08 PM  
**To:** Picone, Katie (katie.picone@novartis.com)  
**Cc:** Gould, Barbara; Williams, Dawn; White, Matthew  
**Subject:** PMRs/PMCs for BLA 125504 COSENTYX (secukinumab)

Dr. Picone,

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We have reviewed your draft package insert (PI), Medication Guide and Instructions for Use (IFUs). The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by October 10, 2014.



BLA  
125504\_Agency ...

We have also reviewed your draft carton and container labeling and our comments are attached. Please resubmit draft carton and container labeling with our comments addressed or your counterproposal by October 10, 2014.



Agency  
Carton\_Contain...

The Agency has identified the following postmarketing requirements (PMRs)/postmarketing commitments (PMCs) to be conducted post approval. Please note that additional PMRs/PMCs may be forthcoming.

### **PREA**

Conduct studies to evaluate the safety and efficacy of secukinumab in pediatric subjects with plaque psoriasis.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

### **Clinical Pharmacology**

PMC Description: Conduct a clinical trial to assess whether secukinumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with secukinumab.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

### **Product Quality**

PMC Description: To re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

PMC Description: To re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

PMC Description: To re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

### **Product Quality Microbiology**

PMC Description: To conduct routine bioburden testing (b) (4)  
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.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

PMC Description: To conduct routine bioburden testing (b) (4)  
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.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

PMC Description: To conduct routine bioburden and endotoxin testing (b) (4)  
. Routine testing will be implemented for the 2015 manufacturing campaign.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

PMC Description: 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.

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

PMC Description: To evaluate feasibility of (b) (4)  
secukinumab drug substance and update drug substance specification (b) (4)

Final Protocol Submission: \_\_\_\_\_  
Study/Trial Completion: \_\_\_\_\_  
Final Report Submission: \_\_\_\_\_

Please submit to your BLA by October 10, 2014 your agreement to conduct the studies above and your timeline for final protocol submission, study completion, and final report submission for each PMR/PMC.

Regards,

J. Paul Phillips, MS  
Regulatory Health Project Manager, Safety

**on behalf of:**

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/

-----  
J P PHILLIPS  
09/26/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing the Product Quality sections of your submission and have the following comments and information requests. We request a prompt written response by September 3, 2014.

1. It is not clear that a risk assessment and appropriate extractables and leachables studies have been performed for the prefilled syringe Drug Product presentation, except with respect to specific testing for (b) (4). Real time leachable studies covering the expiry period should be carried out using representative drug product in the commercial container closure system. Extractables studies should be used to inform the leachables studies, and accelerated leachables studies can be used to provide support for the container closure and expiry period. The leachables analyses should include organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS), and metals (e.g., ICP-MS) species, including their chemical identification and quantitation. Submit information regarding the risk evaluation and studies performed for the prefilled syringe presentation and all available data, or indicate where in the BLA this information resides.
2. The establishments listed on the FORM FDA 356h and additional places in the BLA submission only included the sites involved in testing of the Drug Substance (DS) and Drug Product (DP) themselves and the main manufacturing and packaging processes (e.g., sites for cell bank testing, unprocessed bulk testing, etc.) were not included. Provide a list of all manufacturing, testing and storage sites involved with this submission, starting with the master cell bank.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
08/28/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to February 21, 2014 submission, containing the 120-Day Safety Update for COSENTYX™ (secukinumab).

We are reviewing your safety update and request that you provide additional information on major adverse cardiac events (MACE) to facilitate review. We request a prompt written response by September 3, 2014.

1. Provide in one summary document all subjects that have been unblinded who reported MACE.
2. Provide a table of major adverse cardiac events by indication
3. Provide exposure-adjusted event rates by indication and dose.
4. Provide epidemiological exposure rates of MACE events in patient years for populations studied (e.g., RA, psoriasis) where available.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
08/27/2014

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** August 18, 2014

**Application Number:** BLA 125504

**Product Name:** Cosentyx (secukinumab)

**Applicant Name:** Novartis Pharmaceuticals Corporation

**Subject:** Reference Standard Program

### **FDA Participants**

David Kettl, MD, Clinical Team Leader, DDDP

Sarah Kennett, PhD, Review Chief, DMA

Tura Camilli, PhD, Product Quality Reviewer, DMA

Matthew E. White, Senior Regulatory Health Project Manager, DDDP

### **Applicant Participants**

Diane Zezza, PhD, Global Head Regulatory Affairs CMC

Karen Walker, Quality Head Biologics & BPO Quality

Margaret Casais, Global Regulatory CMC

Mirko Sackewitz, PhD, Late Phase Analytics

Steffen Pahlich, Lab Head Bioanalytics, Biologics-QC

Andreas Balzer, Technical Project Leader

David Jones, Sr. Global Program Regulatory Director

### **DISCUSSION:**

The reference standard program was discussed; specifically the information requested by the Agency in a letter dated August 14, 2014. There was a brief discussion to clarify the Agency's position and the Applicant's proposed responses. The Applicant will submit their official responses to the information requested to the BLA. The discussion ended amicably.

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

/s/  
-----

MATTHEW E WHITE  
08/19/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing the clinical section of your submission and have the following comments and information requests. We request a prompt written response by August 22, 2014.

1. We currently have safety data for ongoing studies up to November 30, 2013. This includes data for 52 weeks of pivotal studies A2302 and A2303; 12 weeks of data for studies A2308 and A2309. Provide a safety update of ongoing studies A2308 and A2390 in support of alternative dose presentations.
2. For ongoing studies across all indications provide a summary update of Deaths and SAEs subsetted by indication and dose.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

AMY S WOITACH

08/15/2014

signing as acting TL on behalf of Dr. David Kettl



BLA 125504

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to your July 31, August 4 and 13, 2014 submissions, containing your responses to the Agency's information requests dated July 22 and August 8, 2014.

We are reviewing the Product Quality sections of your submission and have the following comments and information requests. We request a prompt written response by August 18, 2014.

Regarding Requalification/Stability of Primary and Working Reference Standards:

1. The response to the July 22, 2014 information request and update to section 3.2.S.5 state that working reference standards will be (b) (4)

The Agency does not agree with this approach, because (b) (4)

[Redacted]

[Redacted] (b) (4)

2. Based on the August 13<sup>th</sup> response to the Agency's request for information that states that the acceptance criterion for potency would be tightened to [Redacted] (b) (4)
3. In reference to your response to question 1 received on August 13<sup>th</sup>, we agree to your proposed acceptance criteria of [Redacted] (b) (4) % for the [Redacted] (b) (4) for release and stability of Drug Substance. Submit the revised specification sections to the BLA.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

AMY S WOITACH

08/14/2014

signing as acting TL on behalf of Dr. David Kettl



BLA 125504

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013 received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to your July 31 and August 4, 2014 submissions, containing your responses to the Agency's information request dated July 22, 2014.

We are reviewing your submissions and have the following comments and information requests. We request a written response by August 13, 2014.

1. We do not agree with a number of the proposed acceptance criteria included in the release and stability specifications for secukinumab DS (3.2.S.4.1), secukinumab 150 mg powder for solution for injection (3.2.P.5.1) and secukinumab 150 mg/ml solution for injection in PFS (3.2.P.5.1). Based on statistical analyses performed using calculations of standard deviations and (b) (4)

the changes listed in the tables below are proposed.

**Secukinumab DS:**

	Proposed in BLA for release and stability	Proposed revision for release and stability
(b) (4)		

**DP Secukinumab 150 mg powder for solution for injection:**

	Proposed in BLA for release and stability	Proposed revision for release and stability
(b) (4)		

**DP Secukinumab 150 mg/ml solution for injection in PFS including in the AI:**

	Proposed in BLA for release	Proposed revision for release	Proposed in BLA for stability	Proposed revision for stability
(b) (4)				

2. Regarding the reference standard (response to the July 22, 2014 information request):

a. The response confirms that reference standard lots (b) (4)

[Redacted]

b. The response includes reference to the “(b) (4)” and the “(b) (4)”. We are not familiar with these terms but expect they may refer to the confidence interval for a difference and confidence interval for a ratio. Define these two types of confidence intervals and provide the formulas used to establish both intervals.

3. The integrity of the (b) (4) used as part of the identification of secukinumab in the PFS presentation is critical to the use of this (b) (4) in support of conformance to 21 CFR 610.14. After examination of the PFS sample that was provided to the Agency in July and the diagram in figure 2-1 of the appendix to section 3.2.P.7, the (b) (4) are still unclear. The Description of Manufacturing Process and Process Controls section (3.2.P.3.3) states only that the syringes are labeled with the (b) (4). Provide a description of the (b) (4) and the procedure for adding the (b) (4) to the PFS.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

GARY T CHIANG  
08/08/2014  
Signing as Acting Team Lead



BLA 125504

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013 received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing your submission and have the following comments and information request. We request a written response by August 12, 2014.

- On the signed FDA FORM 356h, you listed [REDACTED] (b) (4) as a testing site for DP Secukinumab PFS and AI QC and stability Break out and sliding force testing. However, based on the FDA's database, [REDACTED] (b) (4) is actually for a different [REDACTED] (b) (4) site. Provide the correct address and FEI number for this testing site.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

GARY T CHIANG  
08/07/2014  
Signing as Acting Team Lead

**PeRC PREA Subcommittee Meeting Minutes  
July 16, 2014**

**PeRC Members Attending:**

Lynne Yao  
George Greeley  
Daiva Shetty  
Wiley Chambers  
Susan McCune  
Rachel Witten  
Shrikant Pagay  
Tom Smith  
Karen Davis Bruno  
Susan McCune  
Rosemary Addy  
Dianne Murphy  
Lily Mulugeta  
Rachel Witten  
Michelle Roth Cline  
Rosemary Addy

## PREA

10:10	BLA	125504	Cosentyx (secukinumab) Partial Waiver/Deferral/Plan	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
-------	-----	--------	---	--

(b) (4)

### **Cosentyx Partial Waiver/Deferral/Plan**

BLA 125504 seeks review of Cosentyx (secukinumab) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

- The application has a PDUFA goal date of January 23, 2015.
- The application triggers PREA as a new active ingredient.
- The Division clarified that there was specific safety concerns with this product in adult trials (e.g., cardiovascular safety concerns) as well as safety concerns for another product in the class (ustekinumab). The PREA requirements for ustekinumab are deferred for several years in order to obtain long-term adult safety data.
- *PeRC Recommendations:*

- The PeRC agreed with the Division to grant a partial waiver in patients ages birth to less than 6 years because studies are impossible or highly impractical and to the deferral because additional safety or effectiveness data is needed.
- The PeRC agreed to defer studies in patients 6 to less than 17 years but there was some disagreement about the length of time to complete the studies. Some PeRC members noted that the safety concern should be addressed with proper controlled studies in children rather than waiting on adult long-term safety data if the current data do not identify a specific pediatric safety concern. Some PeRC members agreed that a long deferral to complete pediatric studies would be acceptable to collect long-term adult safety information but that labeling should reflect that the product is not recommended to be used in pediatric patients if this approach is used.

(b) (4)



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

/s/  
-----

GEORGE E GREELEY  
07/29/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza, Building 135, Office 521  
East Hanover, NJ 07936

Dear Ms. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukimuab).

We are reviewing your submission and have the following comments and information requests. We ask that you respond by July 31, 2014.

I. Regarding the Drug Substance (DS) manufacturing process and process validation:

1.



activities do not affect product quality can be performed using concurrent validation protocols. The protocols should include evaluations of (b) (4)

and reintroduced as part of a post approval submission containing the validation protocols or validation data.

2. Regarding the (b) (4) that were submitted in the April 4 information request response:

a. The (b) (4) does not include acceptance criteria for (b) (4); therefore, the protocol is not complete. Implement acceptance criteria for (b) (4) analyses.

b. The mechanism for determining acceptable membrane efficiency during the course of the (b) (4) study is not clear. (b) (4)

c. The results of the completed (b) (4) studies should be reported in the subsequent annual report.

3. Regarding section 3.2.S.2.2:

a. Submit the updated section to the BLA.

b. The Agency does not agree that some of the parameters or attributes classified by Novartis as non-key do not need to be reported in the submission. While management of the process is under the control of the Novartis quality system, as indicated in Tables 2-1 and 2-2, the description of the process and process controls should be sufficiently complete with respect to parameters that affect or indicate product quality. Novartis indicates that some parameters that are not included have "(b) (4)" or that the operating parameter is acceptable over a wide range or is easy to control; however, these parameters have an impact on the process and should be reported as part of the process. Add the following process parameters and operating ranges/acceptance criteria to section 3.2.S.2.2:

i. (b) (4)



d. (b) (4) are important controls for monitoring process performance; therefore, the controls specified in sections 3.2.S.2.2 or 3.2.S.2.4 should be complete. Regarding the footnotes to Table 4-21 included in the April 4 information response request:

- i. Set initial (b) (4) and other in-process controls using data derived from the manufacturing experience to date.
- ii. Any changes to (b) (4) that are included in sections 3.2.S.2.2 or 3.2.S.2.4 should be reported to the BLA using the reporting category appropriate to the specific parameter and change made.

e. (b) (4)

4. It is known that pausing during (b) (4)  
Based on the description of the validation study performed for the secukinumab (b) (4)  
(b) (4)  
Confirm whether the Agency's understanding of the validation study is correct.

## II. Regarding Control of Materials:

1. Section 3.2.S.2.3.3.2 states that if additional working cell banks (WCBs) are needed, they "will be prepared according to the procedures described above." The protocol(s) for manufacturing and qualification of a new WCB should be submitted to the BLA. If a protocol is not submitted at this time, clarify in the BLA that implementation of any future WCB will be submitted as a prior approval supplement (PAS); the WCB protocol could also be submitted as a PAS. Qualification of a new WCB should include, but not be limited to, analyses of growth characteristics, productivity, viability, and product quality attributes, and the protocol should include manufacturing of commercial scale lots.
2. No data were provided to support the acceptance criteria for viability levels of the master cell bank (MCB) and WCB in response to the March 17 information request; a statement of "prior experience with other monoclonal antibodies cell lines" is not sufficient to support the criteria for the stability of the secukinumab cell banks. The current levels of (b) (4) viability are too low. Revise the acceptance criteria based on secukinumab manufacturing experience.

3. The description of the manufacturing process and control of materials sections do not make clear the types of [REDACTED] (b) (4). This information is necessary to evaluate potential risk from leachables. Provide additional detail regarding the [REDACTED] (b) (4) included in Table 1-8, specifically the materials used for the product contact surfaces of these containers.
4. Section 3.2.S.2.3.2.2.3 states that [REDACTED] (b) (4) was used during production of the secukinumab cell line. The information provided regarding [REDACTED] (b) (4) is that it was compliance with the US regulations "in place at that time" (section 3.2.A.2, Risk assessment – [REDACTED] (b) (4) raw materials in CHO cell line development). To enable a more comprehensive evaluation of the risk assessment provided for the use of [REDACTED] (b) (4), provide a comparison of the regulations in place "at that time" and the current regulations.

III. Regarding the reference standard (RS):

1. Section 3.2.S.5 states that a new primary RS [REDACTED] (b) (4).  
[REDACTED] Confirm that such a requirement is in place.
2. The potency criterion for release of new primary or working RS is not acceptable. The criterion of [REDACTED] (b) (4) is significantly wider than the current expectations for qualification of primary and working RS. Materials in the outer regions of this range are not reflective of the materials that were used in the pivotal clinical studies. In addition, assigning a potency of [REDACTED] (b) (4).  
[REDACTED] (b) (4) Update the requirements to include a sufficiently narrow range(s) for potency at release to ensure that the quality of the commercial DP does not drift from the quality of the material used during the pivotal clinical studies. Note that implementing slightly different ranges for release of primary and working RS might be useful.
3. Regarding potency at the time of retesting:
  - a. The method for determining stability of th [REDACTED] (b) (4).  
[REDACTED] Implement an



negative is not clear. For example, it is assumed that the samples are run at least in duplicate, and there should then be clear procedures for determining whether a sample is positive based on results from each replicate, e.g., what is done if one replicate is above the cut point and the other is below the cutpoint. In addition, the evaluation of robustness cannot be evaluated in a comprehensive manner without an understanding of the allowable variations in the method. Provide the immunogenicity assay protocols (screening/confirmatory and neutralizing) to the BLA. If the assay protocols do not address stability and expiry of critical (b) (4) include all available information regarding the stability of these (b) (4)

2. Regarding the evaluation of drug tolerance that is described in the screening/confirmatory assay validation report amendment 1, it appears that the level of tolerance is not appropriate with respect to the levels of secukinumab that would be present in the clinical serum samples. The results provided indicate that 500 ng/ml of the monoclonal positive control (PC) can be detected in the presence of 6.7 µg/ml secukinumab. However, because the trough concentrations at the time points at which samples were collected for immunogenicity testing are 22.8, 17.7 and 16.7µg/ml for the 150 mg dose and 44.8, 34.4 and 32.7µg/ml for the 300 mg dose at weeks 12, 24 and 52, respectively, the 6.7 µg/ml secukinumab level is not relevant. At 500 ng/ml, the monoclonal PC would not be detected in clinical samples, and no data were provided to identify the level of monoclonal PC that would be detected. For the polyclonal PC, the levels of drug tolerance determined for three separate runs were very different (29.7, 43.0, and 88.8 µg/ml) and only one run shows acceptable drug tolerance with respect to the levels of on board drug for all clinical sampling time points. The inhibitory levels from the three runs were averaged to obtain the reported drug tolerance level. A justification for using the average of these runs should be provided. Currently, it is not clear that the drug tolerance level identified when using the polyclonal PC is appropriate with respect to the levels of on board drug in the clinical samples. If a sufficient explanation for why the polyclonal study calculations and conclusions are appropriate cannot be provided, a PMR for the development of a screening/confirmatory anti-drug antibody (ADA) assay with appropriate levels of tolerance to on board drug might be necessary.
3. Regarding the evaluation of drug tolerance that is described in the neutralizing assay validation report, while the conclusions made are that 2.5 µg/ml ADA can be detected in the presence of 15 µg/ml secukinumab (based on detectability of the PC) and 10 µg/ml ADA can be detected in the presence of 25 µg/ml secukinumab, the levels of secukinumab in clinical samples (identified above) mean that the 15 µg/ml and 25 µg/ml levels of PC are not relevant to the 300 mg dose, and the 15 µg/ml level of PC is not relevant to the 150 mg dose. Therefore, from the data provided, the only conclusion that can be made is that 10 µg/ml ADA might be detected in the clinical samples from subjects dosed at 150 mg. This level of detectability is lower than what is appropriate. In addition, the raw results at the PC concentrations identified as being tolerant to drug at the stated

levels are only 0.001 and 0.002 units below the cut point for the 2.5 µg/ml and 10 µg/ml levels, respectively, so it is not clear that these values would be confirmed if they were evaluated for consistency. Therefore, the drug tolerance of the current assay is not appropriate, and a PMR for the development of a neutralizing ADA assay with appropriate levels of tolerance to on board drug might be necessary.

4. Regarding the confirmatory assay cut point (CCP):

a.  (b) (4)

b.  (b) (4)

5. An evaluation of interference by serum components, such as hemoglobin and lipids, is expected as part of immunogenicity assay validation; however these were not considered as part of the validation studies provided. Provide all available data regarding the possible interference of serum components on the ability of the assay to detect anti-secukinumab antibodies in human serum.

V. Regarding DS and Drug Product (DP) Stability:

1. The DS and DP commitment sections include completion of ongoing stability studies and placing annual lots on stability protocols. Confirm that the tests and acceptance criteria for the ongoing and annual stability protocols will be updated to reflect the final approved stability specifications.
2. The degradation profiles of the liquid and lyophilized DP are important for evaluations of the use of clinical data obtained with the different materials in support of the other. The rates of degradation do not provide a complete picture of the degradation profiles. Provide any available raw data (e.g., chromatograms, electropherograms, and gels from first and last time points), particularly from studies performed under stressed or accelerated conditions, that would allow for a comparison of the degradation pathways of the different DP presentations.



identification is not acceptable. Implement sampling for identity testing after a permanent secukinumab-specific identifier (e.g., complete label or product or lot number) has been added to the vial and syringe.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
07/22/2014

## Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

### BACKGROUND

Please check all that apply:  Full Waiver  Partial Waiver  Pediatric Assessment  Deferral/Pediatric Plan

BLA/NDA#: BLA 125504

PRODUCT PROPRIETARY NAME: Cosentyx

ESTABLISHED/GENERIC NAME: Secukinumab

APPLICANT/SPONSOR: Novartis Pharmaceuticals Corporation

### PREVIOUSLY APPROVED INDICATION/S:

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

### PROPOSED INDICATION/S:

- (1) Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

BLA/NDA STAMP DATE: 10/24/2013

PDUFA GOAL DATE: 1/23/215

SUPPLEMENT TYPE:

SUPPLEMENT NUMBER:

***Does this application provide for (If yes, please check all categories that apply and proceed to the next question):***

***NEW***  ***active ingredient(s) (includes new combination);***  ***indication(s);***  ***dosage form;***  ***dosing regimen;*** or  ***route of administration?***

***Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)***

***\*Yes***  ***No***

***\*PPSR submitted to IND 100418 on 9/21/2012. PPSR inadequate letter sent 3/28/13***

***Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes***  ***No***

***If Yes, PMR # \_\_\_\_\_ NDA # \_\_\_\_\_***

***Does the division agree that this is a complete response to the PMR? Yes***  ***No***

***If Yes, to either question Please complete the Pediatric Assessment Template.***

***If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.***

## WAIVER REQUEST

*Please attach:*

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived.  
Children less than 6 years of age.
2. Reason(s) for waiving pediatric assessment requirements (**Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.**)
  - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
  - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
  - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
  - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)

3. *Provide justification for Waiver:*

- The prevalence of psoriasis in the 0 to less than 6 age group is low (with the highest prevalence published of 0.3%) and the proportion of children with a severe condition in need of a systemic treatment is 4%, giving a final prevalence of the condition to be about 1 per 10,000 in this age group.
- IL-17 is a key mediator of the innate immune response and the potential risk of an impact on the developing innate immune system in this age group should be avoided.
- Live vaccinations (MMR, varicella) are usually given in this age group, limiting the treatment of this pediatric population with secukinumab.

4. *Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:*

The division concurs with the applicant's following proposed language:

Safety and effectiveness of COSENTYX in pediatric patients have not been evaluated

## DEFERRAL REQUEST

Please attach:

*Pediatric Record*

**1. Age groups included in the deferral request:**

6 years to 17 years and 11 months

**2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:**

Waiver as per above

**3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)**

a. Additional safety or effectiveness data needed (**describe**)

Serious safety signals have been observed in clinical trials for this class of agents in patients with arthritis, inflammatory bowel disease and psoriasis that will likely require the deferral of pediatric studies until after adult studies have been completed and additional safety data are collected and reviewed in adult psoriasis patients.

**4. Provide projected date for the submission of the pediatric assessment (deferral date):**

December 1, 2022

**5. Did applicant provide certification of grounds for deferring assessments?  Yes  No**

**6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?  Yes  No**

## SPONSOR'S PROPOSED PEDIATRIC PLAN

**1. Has a pediatric plan been submitted to the Agency?  Yes  No**

**2. Does the division agree with the sponsor's plan?  Yes  No**

**3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?**  Yes  No

Novartis proposes to defer the start of the pediatric study (age group 6 to less than 18 years of age) until after data from a twelve months treatment period from the phase III program in psoriasis adult patients becomes available.

a. **Protocol Submission:**

b. **Study Completion:**

c. **Study Submission:** December 31, 2018

**4. Has a Written Request been issued?**  Yes  No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)

**5. Has a PPSR been submitted?**  Yes  No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

PPSR submitted to IND 100418 on 9/21/2012. PPSR inadequate letter sent 3/28/13

***Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.***

**DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL**

*Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.*

**Types of Studies/Study Design:**

**Nonclinical Studies:**

**Clinical Studies:**

A pharmacokinetic/pharmacodynamic and safety study

A dose ranging study to evaluate different potential doses of secukinumab in different pediatric age groups

A clinical efficacy and safety study in pediatric patients 6-17 years of age

A long-term safety extension study in pediatric patients 6-17 years of age

**Age group and population (indication) in which study will be performed:**

Ages 6- 17 years 11 months

This section should list the age group and population exactly as it is in the plan.

*Example:*

*Study 1: patients aged X to Y years.*

*Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.*

**Number of patients to be studied or power of study to be achieved:**

*Example:*

*Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.*

*Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.*

**Entry criteria:**

*This section should list pertinent inclusion/exclusion criteria.*

*Example:*

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs*

*Patients must have a negative pregnancy test if female..*

<p><b>Clinical endpoints:</b></p> <p><i>Example:</i>  <i>Study 1: Clinical outcome and safety will be the primary endpoints.</i></p> <p><i>Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.</i></p>
<p><b>Timing of assessments:</b></p> <p><i>Example :baseline, week 1, 4, and 6</i></p>
<p><b>Statistical information (statistical analyses of the data to be performed):</b></p> <p><i>Example:</i>  <i>Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.</i></p> <p><i>Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.</i></p>
<p><b>Division comments on product safety:</b></p> <p>Are there any safety concerns currently being assessed? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p>Will a DSMB be required? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>

<i>Other comments:</i>
<b>Division comments on product efficacy:</b>
<b>Division comments on sponsor proposal to satisfy PREA:</b>

<p><b>PeRC ASSESSMENT TEMPLATE</b></p> <p><i>Please attach:</i></p> <ul style="list-style-type: none"> <li><input type="checkbox"/> <i>Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.</i></li> <li><input type="checkbox"/> <i>Pediatric Record</i></li> </ul> <p><b>Date of PREA PMR:</b>  <b>Description of PREA PMR:</b> <i>(Description from the PMC database is acceptable)</i></p> <p>Was Plan Reviewed by PeRC? <input type="checkbox"/> <b>Yes</b> <input type="checkbox"/> <b>No</b> If yes, did sponsor follow plan?</p> <p><b>If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.</b></p> <p><b>Indication(s) that were studied:</b>  This section should list the indication(s) exactly as written in the <i>protocols</i>.</p>
--

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

/s/  
-----

MATTHEW E WHITE  
07/02/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Regulatory Manager  
One Health Plaza  
Building 135, Room 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing the Clinical Pharmacology section of your initial BLA submission and we have the following requests for exposure-response (E-R) analyses. We request a prompt written response by July 14, 2014 in order to continue our evaluation of your BLA.

1. Conduct E-R analyses for the following efficacy endpoints: PASI 75, PASI 90, PASI 100, and IGA 1/0 response rate at Week 12 (primary endpoint) and Week 16 (estimated peak response time based on the observed data). Conduct and compare the analysis using observed concentration and model-predicted exposures for both 150 mg and 300 mg doses. As part of the E-R analyses, compare the efficacy response rates by body weight subgroups, for example, subgroups of [ $< 70$  kg, 70-90 kg, and  $\geq 90$  kg] and subgroups of [ $< 90$  kg and  $\geq 90$  kg]. You may also propose other subgroups using different body weight cutoff strategies. Provide summary tables of the predicted response rates for each efficacy endpoint by doses (150 mg and 300 mg) and by body weight subgroups.
2. We acknowledge your E-R analysis for safety endpoints at Week 12 submitted on June 9, 2014 (Response to FDA Information Request, Tables 3-4 and 3-5). Conduct a similar analysis for concentration of secukinumab and adverse events at Week 52. In the analysis, add Candida infections as a safety endpoint.
3. Submit E-R analysis reports with detailed description of the analysis methods along with all the datasets and scripts used for the analysis.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
06/27/2014



BLA 125504

**MID-CYCLE COMMUNICATION**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Regulatory Manager  
One Health Plaza  
Building 135, Room 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to the teleconference between representatives of your firm and the FDA on June 19, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Matthew White, Senior Regulatory Project Manager at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Mid-Cycle Communication

## MID-CYCLE COMMUNICATION

**Meeting Date and Time:** June 19, 2014 at 11:00 am

**Application Number:** BLA 125504  
**Product Name:** COSENTYX™ (secukinumab)

**Proposed Indication:** Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

**Applicant Name:** Novartis Pharmaceuticals Corporation

**Meeting Chair:** Dr. David Kettl  
**Meeting Recorder:** Matthew White

### FDA ATTENDEES

Julie Beitz, MD, Director, ODE III  
David Kettl, MD, Clinical Team Leader, DDDP  
Amy Weitach, DO, MS, Clinical Reviewer, DDDP  
Mohamed Alesh, PhD, Biostatistics Team Leader, DB III  
Carin Kim, PhD, Biostatistics Reviewer, DB III  
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3  
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3  
Jeffrey Florian, PhD, Acting Pharmacometrics Team Leader, OCP/DPM  
Jee Eun Lee, PhD, Pharmacometrics Reviewer, OCP/DPM  
Sarah Kennett, PhD, Review Chief, DMA  
Tura Camilli, PhD, Product Quality Reviewer, DMA  
Captain Robert Pratt, PharmD, Director Regulatory, DRISK  
CDR Diem-Kieu Ngo, PharmD, USPHS, Supervisor, DACCM  
Kimberly Taylor, Operations Research Analyst, OPA  
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III  
LCDR Richard Ishihara, USPHS, Regulatory Scientist (acting), ODE III  
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP  
Matthew E. White, Senior Regulatory Health Project Manager, DDDP

### EASTERN RESEARCH GROUP

Chelsea (So Hyun) Kim, Independent Assessor

### APPLICANT ATTENDEES

Rob Kowalski, Global Drug Regulatory Affairs Head  
Paula Rinaldi, North America Drug Regulatory Affairs Head  
Penny Giles, Franchise Drug Regulatory Affairs Head  
David A. D. Jones, Sr Global Program Regulatory Director  
Katie Picone, Sr Global Program Regulatory Manager  
John Hohneker, Franchise Development Head  
George Vratsanos, Executive Global Program Head

Jose Maria Gimenez Arnau, Sr Global Program Head  
Charis Papavassilis, Global Program Medical Director  
Ellen McCroskery, Franchise Drug Safety & Epidemiology Lead  
Achim Guettner, Lead Statistical Scientist  
Gerard Bruin, DMPK  
Peter Lloyd, DMPK  
Sebastian Spindeldreher, DMPK  
Diane Zezza, Global Regulatory CMC Head  
Nancy Landzert, Global Regulatory CMC Liaison  
Andreas Balzer, Technical Project Lead

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT REVIEW ISSUES

### Product Quality

Product quality has identified two main issues related to the immunogenicity assay and the identity testing.

- Tolerance of the anti-drug antibody (ADA) assays to drug in the serum samples—potential need for more sensitive neutralizing antibody assay
- Identity testing of the drug product—(b) (4) is not sufficient per 21 CFR 610.14

### Clinical Pharmacology

- Autoinjector comparability issue:

The PK from the prefilled SensoReady pen (Autoinjector) presentation appears not comparable to that from the lyophilized powder in vial. Based on the trough concentrations at Week 4 and Week 12, the autoinjector achieved serum secukinumab concentrations up to approximately 30% higher than the lyophilized powder.

### **Clinical**

- Risk benefit calculus for applicant proposed dosing across various weight cohorts - Potential concerns regarding higher exposure with the autoinjector over maintenance use.

### **3.0 OTHER ISSUES**

- Labeling for PRO endpoints – the applicants labeling proposal may need to be amended
- Pharmacovigilance plan - need for additional information for proposal for (b) (4) registry
- No nonclinical review issues have been identified to date
- Labeling for EU sourced Enbrel comparator from a single trial may not be acceptable

### **Post Meeting Addendum**

In regards to your June 11, 2014 submission, the response about the hold time validation is acceptable. (b) (4)

### **4.0 INFORMATION REQUESTS**

#### **Outstanding information requests:**

- Product Quality/Biostatistics information request dated June 18, 2014

#### **Additional information requests forthcoming:**

- At least one additional information request from Product Quality will be forthcoming
- Additional information request regarding exposure-response analyses for efficacy and safety endpoints forthcoming
- Additional information request regarding study design for (b) (4) registry forthcoming.

### **5.0 MAJOR SAFETY CONCERNS**

- None have been identified at this stage of the review

## 6.0 RISK MANAGEMENT UPDATE

- At this time, no safety concerns have been identified that require a REMS to ensure safe use.

## 7.0 ADVISORY COMMITTEE MEETING PLANS

- Tentatively scheduled for October 20, 2014
- Potential Topics for Discussion:
  - General discussion of safety and efficacy of secukinumab in psoriasis
  - Effect of body weight on efficacy/adequacy of dose ranging
  - Effect of product presentation on efficacy
  - Comparability of autoinjector data to lyophilized powder in vial and potential safety impacts of exposure-response data

## 8.0 POTENTIAL PMC/PMR'S

- Develop a neutralizing ADA assay with better drug tolerance
- In vivo drug-drug interaction studies in subjects with psoriasis to evaluate the psoriasis disease-DDI potential between secukinumab and certain CYP substrates.

*(PMC/PMR to conduct psoriasis disease-Drug Drug Interaction study(ies): Psoriasis disease condition involves elevated proinflammatory cytokines which can suppress CYP450 enzymes. And, secukinumab treatment can alleviate the inflammatory condition thereby affect the CYP enzymes and the PK of CYP enzyme substrates. So far, no drug-drug interaction studies have been conducted with secukinumab in subjects with psoriasis.)*

- Potential need for additional information to optimize the dosing regimen for subjects with higher (>90kg) body weight
- PREA PMR—Likely waiver under 6 years of age; deferral of further studies for ages 6-17 until after adult studies have been completed and a determination of safety and efficacy has been made for adult psoriasis subjects as per the April 5, 2013 advice letter.

### **Post Meeting Addendum**

The following additional potential PMCs have been identified:

- Conduct routine bioburden testing [REDACTED] (b) (4)  
[REDACTED] The bioburden method will be qualified with samples

during the 2015 secukinumab manufacturing campaign. Routine testing will be implemented for the 2016 manufacturing campaign.

- Conduct routine bioburden testing [REDACTED] (b) (4)  
[REDACTED] The bioburden method will be qualified with samples from the 2015 production batches. Routine testing will be implemented during the 2016 manufacturing campaign.
- Conduct additional microbial quality (bioburden and endotoxin) hold time validation studies on two batches at commercial scale [REDACTED] (b) (4)  
[REDACTED] during the 2015 and 2016 secukinumab manufacturing campaigns.

#### **9.0 PROPOSED DATE FOR LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES**

- Date range for Late Cycle Meeting: September 19 – October 8, 2014

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

/s/  
-----

DAVID L KETTL  
06/24/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Regulatory Manager  
One Health Plaza  
Building 135, Room 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing the clinical section of your initial BLA submission and have the following comments and information requests. We request a prompt written response by July 2, 2014 in order to continue our evaluation of your BLA.

1. Clarify why the dictionary derived or preferred term (AEDECOD) for vascular adverse event terms stroke and myocardial infarction are missing. We request that you provide a summary of these events and clarify why none of these are reported as serious.
2. In all 4 studies, there are records of adverse events (AE) that do not identify whether the AE is serious (No qualifiers set to 'Y', when AE is Serious.) and the information is not collected in the CRF. The SUPPAE domain indicates that serious events occurred, as there is a reference to a "Date SAE report submitted to Novartis". Provide full documentation for these serious adverse events.
3. Provide shift tables between normal, Stage I, and Stage II BPs, and K-M curves showing time to first BP above those cutoffs.
4. Provide any additional updated information on subject AIN457A2302-20110004 or AIN457A2309-8001006 if available.
5. Provide additional information on the proposed (b) (4) registry.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
06/19/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Regulatory Manager  
One Health Plaza  
Building 135, Room 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing your submission and have the following information requests. We request a prompt written response by June 30, 2014 in order to continue our evaluation of your BLA.

### Product Quality

1. Provide the dye ingress test result summary for vials evaluated for container closure integrity using maximum, minimum and target operating crimping conditions.

2. Clarify if

(b) (4)

### Biostatistics

3. The Agency would like clarification concerning the randomization procedure that was conducted in the trials. According to your protocol, you stated that "At Visit 2, all eligible subjects would be randomized via the Interactive Response Technology (IRT) to one of the treatment arms." Further, your protocol specified that "the investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria." Our understanding is that the randomization occurred after the investigator contacted the IRT. However, your "Documentation of statistical methods

(Appendix 16.1.9) specified that “misrandomized subjects included subjects who were screen-failures, but had been randomized by the investigator before eligibility was finally assessed, however, had not been treated.” Clarify whether randomization was carried out by the IRT or by the investigator. In addition, for each mis-randomized subjects, provide detailed information on how and when the mis-randomization occurred including the treatment assignment.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
06/18/2014



BLA 125504

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Regulatory Manager  
One Health Plaza  
Building 135, Room 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to your March 12, 2014 submission, containing your response to the Agency's March 4, 2014 information request.

We are reviewing the Microbial Quality-Drug Substance section of your initial BLA submission and have the following comments and information requests. We request a prompt written response by June 11, 2014 in order to continue our evaluation of your BLA.

1. Description of the Manufacturing Process and Process Controls

- a. [REDACTED] (b) (4)
- b. Monitor bioburden or conduct [REDACTED] (b) (4)

2. Control of Critical Steps and Intermediates

- a. [REDACTED] (b) (4)  
Submit microbial quality results for the maximum hold time validation study.  
Conduct microbial quality sampling of the [REDACTED] (b) (4)  
[REDACTED] at the end of the hold.

3. Process Validation and/or Evaluation – In-Process Hold Validation

- a. Validate maximum hold times in triplicate at commercial scale for (b) (4) and submit the validation report. (b) (4), maximum hold times can be validated by demonstrating integrity of the vessels during the hold time using (b) (4).
- b. (b) (4)
- c. Clarify if drug substance sampling is conducted (b) (4).

4. Analytical Procedures

- a. Describe how the (b) (4) test is routinely conducted for release samples; include sample volume, if samples are diluted prior to (b) (4), composition of (b) (4) and what is the final volume of sample plated taking (b) (4) into account; include also media and incubation conditions.
- b. Describe how the (b) (4) method is conducted for in-process and release samples; include number of replicates for samples and standard curve, concentrations used for the standard curve, spike endotoxin concentration for the product positive control, and dilutions used for routine testing. Indicate if (b) (4) is used for routine endotoxin testing and specify the concentration and in which samples is used.

5. Validation of Analytical Procedures – Verification of Endotoxin Test

- a. Indicate if there is any difference, other than addition of (b) (4), between the local procedure used for verification of in-process sample endotoxin test and the compendial test (USP <85>); clarify if the local method includes acceptance criteria for the standard curve coefficient of regression and for the negative control. Indicate which batches of in-process samples were used for the in-process sample endotoxin verification test.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
05/29/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Regulatory Manager  
One Health Plaza  
Building 135, Room 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing the Product Quality section of your initial BLA submission and have the following comments and information requests. We request a prompt written response by June 11, 2014 in order to continue our evaluation of your BLA.

1. The Description of Manufacturing Process and Process Controls sections (3.2.P.3.3 for lyophilisate in vial and prefilled syringe) need to include more comprehensive descriptions of the manufacturing processes to ensure that the processes remain under appropriate control. Inclusion of descriptive information in the development or validation sections (3.2.P.2 and 3.2.P.3.5, respectively) is not sufficient. Revise the description of the drug product (DP) manufacturing process section (3.2.P.3.3), or Control of Critical Steps and Intermediates sections (3.2.P.3.4), where appropriate, to include additional process parameters and the corresponding operating ranges or control limits; sufficient information regarding the equipment used should also be included. We note that Tables 5-1 through 5-4 and Table 5-7 in the Process Validation and/or Evaluation section (3.2.P.3.5) for the lyophilized DP includes the type of information that should be included in section 3.2.P.3.3/3.2.P.3.4; we suggest basing the revisions on this table. Operating ranges should be supported by process development and validation data that are included in the BLA.
2. Operational and performance parameters appear to be described only in the process validation sections (3.2.P.3.5). The definition of the parameter types and the designation of the parameter types for the parameters included in the description of

manufacturing process and control of critical steps sections (3.2.P.3.3 and 3.2.P.3.4) should be included in those sections, as appropriate, because these are the sections that provide information regarding the processes and controls that will be used for future manufacturing. In addition, information regarding the actions taken when the operating ranges and control limits/criteria are not met should be provided in these sections, as appropriate. Update the BLA to include this information.

3. The Pharmaceutical Development section 3.2.P.2.3.1.3.1.1 (prefilled syringe; cross-referenced for lyophilisate) includes a statement that (b) (4)  
" If this option is to be included for commercial manufacturing, it should be included in sections 3.2.P.3.3, and data should be provided to support the lack of impact on quality attributes.
4. Due to the differences between the drug substance (DS) and DP formulations, the DP (b) (4) needs to be prepared specifically for each batch of DP (b) (4). In sections 3.2.P.3.2 (Batch Formula) and 3.2.P.3.3, it is not clear how the concentration of DS is determined. Provide additional information in these sections of the BLA to clarify this process.
5. Throughout much of the manufacturing process development sections (3.2.P.2.3, prefilled syringe and lyophilisate), data are not provided to support the parameters selected based on, for example, homogeneity and unchanged quality attributes. Provide data for studies performed for steps including (b) (4)  
Where appropriate, data should be provided from samples taken from (b) (4).
6. In-use conditions are described for the reconstituted lyophilisate based on the stability studies that were performed (section 3.2.P.2.6); however, the results of these studies were not provided. Submit the data from the stability studies in support of the proposed conditions for storage of the reconstituted lyophilisate.
7. Similarly to the manufacturing process development sections, the process validation sections (3.2.P.3.5, prefilled syringe and lyophilisate) contain little data from the validation studies in support of validation of the manufacturing processes. Provide data, including the actual operating conditions and quality data for steps including (b) (4). The BLA should include sufficient data to demonstrate consistency of product quality throughout the filling process. Pre- and post-hold quality data should be provided in support of proposed hold times.

8. For the validation of the lyophilization process performance, the data provided in section 3.2.P.3.5 table 7-2 as an “overview of analytical data of lyophilized vial” lists ranges for the different parameters evaluated in all four batches analyzed. It is unclear what the data ranges represent. Clarify the source of these data, specifically if the data correspond to batch analysis results or if the data represent the results of testing performed by placing the vials on different shelves and locations in the lyophilizer. If the data correspond to batch analysis results, provide all available data from on vials placed on different shelves and locations in the lyophilizer.
9. It is not possible to evaluate degradation pathways, in addition to degradation rates, based on tabular stability data. Provide the raw data (e.g., gels, chromatograms, electropherograms) for the initial time point and the last available time for the DS and DP stability studies to allow for a more comprehensive evaluation of the stability of secukinumab.
10. The February 5, 2014 response to comment #1 from the Day 60 letter (December 17, 2013) indicates that a (b) (4) is intended to be used for a marker of identity for the pre-filled syringe. We do not agree that this is an appropriate identifier for the DP with respect to the requirements of 21 CFR 610.14. While the Agency has accepted, for example, lot numbers printed on vial crimps in lieu of the vial/syringe label, (b) (4) is not considered sufficiently unique; reasons for this determination include, for example, the potential for (b) (4) to be altered by the manufacturer of the marker and the subjectivity of the identification. In addition, the identity testing for the vial DP was not addressed in this response. Provide detailed information regarding the identity testing and confirm that it meets the CFR requirements.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
05/23/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Regulatory Manager  
One Health Plaza  
Building 135, Room 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing the Clinical Pharmacology section of your initial BLA submission and have the following comments and information requests. We request a prompt written response by June 9, 2014 in order to continue our evaluation of your BLA.

- You proposed to register three secukinumab formulation(s)/presentation(s) in your BLA application: prefilled autoinjector/pen (AI), prefilled syringe (PFS), and lyophilized powder in vial (LYO). You conducted two pivotal Phase 3 trials (CAIN457A2302 and CAIN457A2303) with LYO, one Phase 3 trial with PFS (CAIN457A2308), and one Phase 3 trial (CAIN457A2309) with AI. To support the registration of AI or PFS, you should demonstrate its comparability to LYO. You have conducted a bioequivalence trial (CAIN457A2106) which may support the comparability between PFS and LYO. We are concerned that the AI presentation may not be comparable to LYO or PFS.
- We conducted a cross-study comparison of secukinumab trough concentrations in the above mentioned four Phase 3 trials. Results showed that, in comparison to the concentrations observed with LYO, the concentrations resulting from AI appeared to be approximately 10% - 30% higher across the two doses (150 mg and 300 mg) and two PK timepoints (Week 4 and Week 12). Consistently, the secukinumab trough concentrations resulting from AI were approximately 16% - 26% higher than these from PFS. The primary efficacy results further showed that AI appeared to have numerically higher response rates for both IGA 0/1 and PASI 75 than LYO, particularly for the proposed 300 mg dose.

- We request that you provide explanations for why the secukinumab trough concentrations resulting from AI were higher than those from LYO. We request you conduct an exploratory analysis comparing the trough concentrations for LYO and AI following the methodology for bioequivalence assessment and calculate the geometric mean ratio between LYO (reference) and AI (test). Submit PK analysis reports with detailed description of the methods used for the analysis and submit all the PK datasets used for the PK analysis.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
05/22/2014



BLA 125504

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

ATTENTION: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act, for Secukinumab, 150 mg/vial; Secukinumab, 150 mg/mL PFS and Secukinumab, 150 mg/mL auto-injector.

We also refer to:

- Our email dated February 10, 2014, requesting submission of your proprietary name under the BLA
- Your correspondence dated February 10, 2014, stating the proprietary name was submitted on October 22, 2013, and our email response requesting that you submit, in a separate submission, a request for a proposed proprietary name review
- Your correspondence, dated and received February 12, 2014, requesting review of your proposed proprietary names, Cosentyx and Cosentyx Sensoready Pen

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

We note that in your request for name review submission you presented your proposed proprietary name, Cosentyx Sensoready Pen with a capital letter 'R'. This mixed case presentation (tall man lettering) is typically reserved for differentiating look-alike names that have been confused in the marketplace. Since Cosentyx Sensoready Pen is not a name that has been involved in drug name confusion or wrong drug errors, the letter "r" in the name should not be capitalized in your labels and labeling.

If **any** of the proposed product characteristics as stated in your February 12, 2014, submission are altered prior to approval of the marketing application, the proprietary names should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application, contact Matthew White, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4997.

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

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

/s/  
-----

TODD D BRIDGES on behalf of KELLIE A TAYLOR  
05/12/2014

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:katie.picone@novartis.com)  
**Subject:** (b) (4) for the Delta Autoinjector in support of BLA 125504 for Cosentyx (secukinumab)  
**Date:** Thursday, April 10, 2014 9:58:00 AM

---

Dr. Picone,

In regards to Medical Device Master File (MAF) (b) (4), the following information has been requested from (b) (4) Autoinjector in support of BLA 125504.

You have indicated that after the injection, the needle shield is automatically locked to prevent needle stick injury. However, MAF (b) (4) did not appear to contain testing for a sharps injury prevention feature according to Guidance for Industry and FDA Staff- Medical Devices with Sharps Injury Prevention Features, 2005. Indicate where this information may be found in the MAF or provide the data for review.

You should be notified when MAF (b) (4) is amended in accordance with 21 CFR 314.420(c).

Please contact me if you have any questions.

Regards,

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)  
**Phone:** 301-796-4997  
**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
04/10/2014



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Regulatory Manager One Health Plaza  
Building 135, Room 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to amendments dated December 23, 2013; January 15 and 30, 2014.

We are reviewing the responses to the product quality - drug product section of your submission and have the following information requests. We request a prompt written response by April 4, 2014 in order to continue our evaluation of your BLA.

### Vials and Pre-filled syringes:

Provide the protocol you plan to use for (b) (4) for commercial process including quality attributes that are determined (b) (4)

### Vials:

1. The initial qualification report for (b) (4) 303A0311 is in German. Explain how you evaluate the performance of the (b) (4) and the (b) (4) vials. A short summary of the procedure, acceptance criteria and results should be provided.
2. The Table 1-1 is entitled endotoxin recovery from (b) (4) (amendment dated 1/15/2014), but shows results for (b) (4). Provide details of the bioindicator

used for initial qualification of the (b) (4) and how endotoxin recovery results were obtained from kill of bioindicators.

3. (b) (4)
4. Provide the bacterial concentration at the end of the challenge for (b) (4) validation.
5. In regards to shipping of vials, provide the following:
  - (a) Details of the qualified refrigerated containers used for shipping along with the transport route and mode(s)
  - (b) Clarify if the container is equipped with a cooling and/or heating device
  - (c) Provide the temperature mapping studies performed using commercial load patterns
  - (d) A summary describing handling of the containers
  - (e) Shipping data for process validation lots
6. Microbiological studies in support of the storage time of (b) (4) have not been provided. Provide a summary of a risk assessment and a report from studies that show adventitious microorganism do not grow under the storage conditions for the (b) (4). The report should describe test methods and results that employ a minimum countable inoculum to simulate potential microbial contamination that may occur during product dilution and storage. It is generally accepted that growth is evident when the population increases more than 0.5 Log<sub>10</sub>. The test should be run at the label's recommended storage conditions and be conducted for 2 to 3-times the label's recommended storage period and using the label recommended fluids. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections.
7. You have included information and validation of the (b) (4) for detection of pyrogens in the secukinumab drug product. Clarify if you plan to use the test for release of drug product.
8. Indicate the date when the final report from the low endotoxin recovery studies will be submitted.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
03/26/2014



BLA 125504

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, Pharm D  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to your January 31, 2014 submission, containing your responses to the potential review issues identified in the December 17, 2013 filing communication.

We are reviewing these responses and have the following information requests. We request a written response by March 28, 2014 in order to continue our evaluation of your BLA.

**Regarding Control of Material:**

1. Insufficient information to support [REDACTED] (b) (4) was included in the January 31, 2014 response to the December 17, 2013 filing communication.
  - a. Regarding the [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

**4 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page**

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
03/17/2014



BLA 125504

**INFORMATION REQUEST**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Ms. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We are reviewing the Microbial Quality - Drug Substance sections of your initial BLA submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your BLA by March 12, 2014.

**1. Description of the Manufacturing Process and Process Controls**

- a. Provide a diagram of the manufacturing process and indicate for each step at which point the following events take place:

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



**2. Control of Critical Steps and Intermediates**

- a. [Redacted] (b) (4)
- b. [Redacted]
- c. [Redacted]
- d. [Redacted]

**3. Process Validation and/or Evaluation – Validation Batches**

- a. The process validation batches genealogy is not clear (refer to section 3.2.D.2.5, Table 1-3). Clarify if each batch number is unique. Clarify if each process validation batch is conducted from beginning to end, or if one process validation batch is manufactured using multiple batches coming from different steps. Clarify if the routine production process will be conducted using the same batch from beginning of cell culture to end of purification.
- b. Submit results for all critical in-process control steps of the process validation batches, including microbial quality (bioburden and endotoxin) and [Redacted] (b) (4)

**4. Process Validation and/or Evaluation – [Redacted] (b) (4)**

- a. Describe the studies conducted to evaluate maximum hold times [Redacted] (b) (4) for microbial quality (endotoxin and bioburden) and submit data. Total hold time between two [Redacted] (b) (4) for all steps should be validated for microbial quality at manufacturing scale in triplicates unless a valid justification is provided.
- b. Submit maximum hold time after [Redacted] (b) (4) and indicate if it has been validated for microbial quality.

**5. Shipping Validation**

- a. The diagram describing the location [Redacted] (b) (4)
- b. Submit summary of the routine shipping procedure for secukinumab DS; indicate:
  - i. [Redacted] (b) (4)
  - ii. [Redacted] (b) (4),
  - iii. Maximum and minimum load.
- c. Submit specifications and specification justifications for the maximum time [Redacted] (b) (4) allowed after [Redacted] (b) (4).
- d. Indicate if shipping validation of the loaded container was conducted using real time shipping conditions by shipping [Redacted] (b) (4) [Redacted] (b) (4)

- e. Indicate if validation of (b) (4) integrity (visual leakage) was conducted using the minimum load and actual shipping conditions.

**6. Analytical Procedures**

- a. Describe the microbial enumeration test and endotoxin analytical methods.
- b. Describe the bioburden method used for in-process samples.

**7. Validation of Analytical Procedures – Verification of Microbial Enumeration Test**

- a. Provide concentration of (b) (4) drug substance.
- b. Justify the (b) (4) is conducted during routing (b) (4).
- c. Indicate if growth promotion was conducted as part of the (b) (4).
- d. Indicate if bioburden test used for in-process samples has been verified and submit summary report and results for all in-process sample steps.

**8. Validation of Analytical Procedures – Verification of Endotoxin Test**

- a. Provide concentrations used for the standard curve.
- b. Indicate how positive and negative controls for the system suitability test were prepared.
- c. Indicate if endotoxin test used for in-process samples has been verified and submit summary report and results for all in-process sample steps.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
03/04/2014

## Thomas, Teena

---

**From:** Picone, Katie <katie.picone@novartis.com>  
**Sent:** Wednesday, February 12, 2014 11:35 AM  
**To:** Thomas, Teena  
**Cc:** Anderson, Janet  
**Subject:** RE: BLA 125504

Hi Teena,

As mentioned in my voicemail, since I have already submitted it to module 1.12.4, I will resubmit as 'replace' and include a cover letter with the title mentioned below.

Could you clarify what was the correct approach I should have taken with the original submission? Should it not have been in module 1.12.4 as you mentioned in an previous email? I apologize for the confusion.

Thanks,  
Katie

**Katie Picone, PharmD**

Sr. Global Program Regulatory Manager  
DRA, Integrated Hospital Care (IHC)  
Novartis Pharmaceuticals Corporation  
One Health Plaza (135/521)  
East Hanover, NJ 07936-1080  
USA

Phone +1 862 778 2574  
Fax +1 973 781 8364

(b) (4)

[katie.picone@novartis.com](mailto:katie.picone@novartis.com)  
[www.novartis.com](http://www.novartis.com)

---

**From:** Thomas, Teena [mailto:Teena.Thomas@fda.hhs.gov]  
**Sent:** Wednesday, February 12, 2014 11:20 AM  
**To:** Picone, Katie  
**Cc:** Thomas, Teena; Anderson, Janet  
**Subject:** RE: BLA 125504

Hi Katie,

Thank you for the response. Please refer to page 16 from the link below for the information you requested. The name should be submitted to 1.12.4 as mentioned in the guideline.

Submit a new request for a proprietary name review that includes all required information as detailed in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Let me know if you have any questions.

Thank you,

Teena

---

**From:** Picone, Katie [<mailto:katie.picone@novartis.com>]  
**Sent:** Wednesday, February 12, 2014 11:08 AM  
**To:** Thomas, Teena  
**Cc:** Anderson, Janet  
**Subject:** RE: BLA 125504

Dear Teena,

I will be sure to submit ASAP. Could I clarify what module the information should be submitted? Should I place all documents in the same module as the cover letter and form?

Thanks,  
Katie

**Katie Picone, PharmD**  
Sr. Global Program Regulatory Manager  
DRA, Integrated Hospital Care (IHC)  
Novartis Pharmaceuticals Corporation  
One Health Plaza (135/521)  
East Hanover, NJ 07936-1080  
USA

Phone +1 862 778 2574  
Fax +1 973 781 8364  
(b) (6)  
[katie.picone@novartis.com](mailto:katie.picone@novartis.com)  
[www.novartis.com](http://www.novartis.com)

---

**From:** Thomas, Teena [<mailto:Teena.Thomas@fda.hhs.gov>]  
**Sent:** Wednesday, February 12, 2014 10:50 AM  
**To:** Picone, Katie  
**Cc:** Thomas, Teena; Anderson, Janet  
**Subject:** RE: BLA 125504

Hi Katie,

I just got a response from the review Division. I was advised to inform to resubmit the proprietary name. Please submit the name as soon as possible to the Global Submit and make sure have a cover letter with a title "**REQUEST FOR PROPRIETARY NAME REVIEW**". Let me know if you have any questions. Sorry for the inconvenience.

Thank you,

Teena

---

**From:** Picone, Katie [<mailto:katie.picone@novartis.com>]  
**Sent:** Monday, February 10, 2014 7:57 PM  
**To:** Thomas, Teena  
**Cc:** Anderson, Janet; Makela, Cristina  
**Subject:** RE: BLA 125504

Dear Teena,

Thank you for reaching out with this concern. As part of the original BLA application 125,504 SN 000, module 1.12.4, we submitted the attached request for “Cosentyx” for secukinumab and “Cosentyx Sensoready pen” for the Autoinjector form. In my review of the guidance, I believe we have provided all of the information requested. Would you be able to clarify what may be missing from this request? Or is it that the submission needs to be a separate amendment to the original BLA and not contained within the original BLA?

Any guidance you could provide would be helpful.

Thank you,  
Katie

**Katie Picone, PharmD**  
Sr. Global Program Regulatory Manager  
DRA, Integrated Hospital Care (IHC)  
Novartis Pharmaceuticals Corporation  
One Health Plaza (135/521)  
East Hanover, NJ 07936-1080  
USA

Phone +1 862 778 2574  
Fax +1 973 781 8364

(b) (6)

[katie.picone@novartis.com](mailto:katie.picone@novartis.com)  
[www.novartis.com](http://www.novartis.com)

---

**From:** Thomas, Teena [<mailto:Teena.Thomas@fda.hhs.gov>]  
**Sent:** Monday, February 10, 2014 3:02 PM  
**To:** Picone, Katie  
**Cc:** Anderson, Janet; Makela, Cristina; Thomas, Teena  
**Subject:** BLA 125504

Hi Dr. Picone,

The Division of Dermatology and dental Products(DDDP) is reviewing your BLA 125504 for Secukinumab and came to know that you haven't submitted a proprietary name for this BLA. If you plan to submit the proprietary name for the BLA please submit as soon as possible. Please note that the Proprietary name “Cosentyx” was conditionally accepted under the IND and you still need to submit a proprietary name under the BLA.

Submit a new request for a proprietary name review that includes all required information as detailed in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Please feel free to contact me if you have any questions.

Thank you,

Teena

Teena Thomas, Pharm.D, CGP  
Safety Regulatory Project Manager  
FDA, CDER  
Office of Surveillance and Epidemiology  
Bldg.22, Room 3461  
10903 New Hampshire Ave.  
Silver Spring, Maryland 20993-0002

Tel: 301.796.0549

E-mail : [teena.thomas@fda.hhs.gov](mailto:teena.thomas@fda.hhs.gov)

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

/s/  
-----

TEENA THOMAS  
02/14/2014



BLA 125504

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

On January 15, 2014, we received your January 15, 2014, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 23, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 26, 2014. Furthermore, the new planned date for our internal mid-cycle review meeting is May 16, 2014.

If you have any questions, call Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, MD, FAAD  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

STANKA KUKICH

02/03/2014

Signing for Susan Walker, Division Director



BLA 125504

## INFORMATION REQUEST

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your biologics license application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351 of the Public Health Service Act for COSENTYX™ (secukinumab).

We have reviewed your application, in reference to applicable 21 CFR 820 regulations and the manufacturing of the finished combination product and have determined that the following information is necessary to review your application:

1. Provide the design control procedure covering the Design Input, Design output and Design Validation/Verification, including design changes, for the overall finished combination product.
2. Provide for review information regarding the establishment of a CAPA system compliant with 21 CFR 820.100.
3. Provide details on the manufacturing responsibilities of [REDACTED] (b) (4)

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>.

We request a written response to the items enumerated above by January 31, 2014 in order to continue our evaluation of your BLA. If your response to this information request is determined to constitute a major amendment, you will be notified of this decision in writing. Review of the other sections of your application not mentioned above is continuing.

If you have any questions, please contact the Regulatory Project Manager, Matthew White, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

DAVID L KETTL  
01/21/2014



BLA 125504

**FILING COMMUNICATION –  
FILING REVIEW ISSUES IDENTIFIED**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) dated October 22, 2013, received October 24, 2013, submitted under section 351(a) of the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to your amendment dated November 12, 2013.

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. The review classification for this application is **Standard**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is October 24, 2014.

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 September 24, 2014. In addition, the planned date for our internal mid-cycle review meeting is April 9, 2014. We are currently planning to hold an advisory committee meeting to discuss this application.

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



We request that you submit the following information:

**Biostatistics:**

1. For Studies A2302 and A2303, there were 10 common investigators, and the trials were conducted simultaneously. It's not clear how patient allocation to each trial was determined. For each common investigator, provide detailed information on how such patient allocation to each trial was made.
2. Although the applicant provided the overall efficacy and safety analysis results by gender, race, and age subgroups on the pooled data as part of the ISE and ISS, it would be useful for the applicant to provide study-level subgroup analysis results, as this would enable assessing the consistency (or lack thereof) in any subgroup analysis findings across trials.

**Clinical:**

3. Provide a summary of reported adverse events for autoimmune diseases or provide the location of this information in the current submission. Include both systemic (e.g. lupus, vasculitis, sarcoidosis, antiphospholipid syndrome and inflammatory myopathies) and organ-specific (e.g. interstitial lung disease, uveitis, optic neuritis, peripheral neuropathies, multiple sclerosis, psoriasis, inflammatory bowel disease and autoimmune hepatitis) autoimmune processes.

**Regulatory:**

4. The deferral request in your pediatric plan does not contain evidence that the deferred studies are being conducted or will be conducted with due diligence and at the earliest time possible per FDCA Section 505B(a)(3). Resubmit your pediatric plan with the certification required by FDCA Section 505B(a)(3).

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

- In the Highlights of Prescribing Information, there is white space between the product title and the Initial U.S. Approval.

We request that you resubmit labeling (Microsoft Word format) that addresses these issues by January 6, 2014. The resubmitted labeling will be used for further labeling discussions.

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.

## **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, and Instructions for Use. 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, and Instructions for Use, and you believe the labeling is close to the final version.

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

## **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

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

If you have any questions, call Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, MD, FAAD  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

SUSAN J WALKER  
12/17/2013

**From:** White, Matthew  
**To:** [Picone, Katie \(katie.picone@novartis.com\)](mailto:katie.picone@novartis.com)  
**Cc:** [Gould, Barbara](#)  
**Subject:** BLA 125504 for Cosentyx (secukinumab): Discussion points for December 11, 2013 teleconference  
**Date:** Tuesday, December 10, 2013 12:51:00 PM

---

Dear Dr. Picone,

Please see the below list of information being requested for the review of BLA 125504 for Cosentyx (secukinumab). This information is being provided to you in preparation for the December 11, 2013 teleconference between Novartis and the Division of Dermatology and Dental Products.

**Manufacturing Schedule:**

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

**Vial Presentation:**



requalification of (b) (4)  
on (b) (4)

11. Please provide summary data for the initial qualification and most recent requalification for (b) (4) 303A0334 and 303A0335. The placement of biological indicators in addition to (b) (4) should be provided.
12. Please provide the initial qualification and most recent requalification data for (b) (4) used in the secukinumab process. Clarify if the (b) (4).

(b) (4) Validation:

13. Please provide the study report on the evaluation of viability of (b) (4) validation studies. In addition, the bacterial concentration at the beginning and end of the challenge (b) (4) validation should be provided.

Media Fill:

14. Please provide a summary of your media fill program and the most recent 2012-2013 media fill for (b) (4) and environmental monitoring summary data. The line speeds used for media fills in relation to routine filling process should be provided.

Hold Times:

15. Please provide the hold times for drug product manufacturing process steps for the process validation lots.
16. (b) (4)

Shipping:

17. Please provide summary data from shipping validation studies using minimum and maximum loads of vials and commercial shipper. The location of temperature monitoring sensors within the shipper should be specified. Data covering summer and winter profiles and shipping summary data for the process validation lots should be provided.

- (b) (4) .
18. Please provide the conditions under which (b) (4) drug product will be performed.

**Pre-filled Syringe Presentation:**

Hold Times:

19. Please provide the hold times for drug product manufacturing process steps for the process validation lots.

- (b) (4) .
20. Please provide the protocol and summary data for the initial qualification of the (b) (4)

(b) (4)  
21. Please provide summary data for the initial qualification and most recent qualification for (b) (4) at station 303B7227 and 303A7123.

Filling machine:

22. Please provide summary data for the initial qualification of (b) (4). A diagram showing placement of (b) (4) and biological indicators should be included.

(b) (4)

(b) (4)

Media fill:

25. Please provide the table comparing process parameters monitored during media fill and routine filling of secukinumab drug product in syringes.

Container closure integrity:

26. Please clarify what positive control is used in the container closure integrity test for the stability program. In addition, explain how analysts are qualified for the visual inspection of the container closure in the dye ingress test.

27. Please provide data to demonstrate that there is no sterility breach due to plunger movement during shipping.

Shipping:

28. Please provide summary data from shipping validation studies using minimum and maximum loads of pre-filled syringes and commercial shipper. The location of temperature monitoring sensors within the shipper should be specified. Data covering summer and winter profiles and shipping summary data for the process validation lots should be provided.

**Both vial and syringe presentations:**

(b) (4)  
29. Please clarify i (b) (4) the bioburden and endotoxin limits for the (b) (4) if any, should be provided.

Pyrogen Testing:

30. For biological products, 21 CFR 610.13(b) requires a rabbit pyrogen test. The requirement in 21 CFR 610.13(b) may be waived if a method equivalent to the rabbit pyrogen test is demonstrated in accordance with 21 CFR 610.9. Please provide the protocol and data from the rabbit pyrogen testing of 3 lots of drug products for the vial and pre-filled syringe formulations.

Sterility test:

31. Please provide the data for growth promotion of media used in the sterility test validation.

Autoinjector:

32. Please provide a summary of the risk assessment performed and data to support the statement that the integrity of the pre-filled syringe is not impacted by the assembly process.

Endotoxin recovery:

33. Secukinumab drug product contains excipients (e.g., polysorbate) that could result in low endotoxin recovery (LER) (see K.L. Williams, "Endotoxin Test Concerns of Biologics," American Pharmaceutical Review, October 28, 2013). To determine if endotoxin recovery is affected by the polysorbate-containing secukinumab drug product formulation, undiluted drug product should be spiked with endotoxin, and satisfactory endotoxin recovery demonstrated over time. The studies should be conducted in the same type of containers (b) (4) ) in which the product and samples are held prior to endotoxin testing.

Sincerely,

*Matthew White*

Regulatory Project Manager  
Division of Dermatology and Dental Products  
Center for Drug Evaluation and Research  
Food and Drug Administration

**E-mail:** [matthew.white@fda.hhs.gov](mailto:matthew.white@fda.hhs.gov)

**Phone:** 301-796-4997

**Fax:** 301-796-9895

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

/s/  
-----

MATTHEW E WHITE  
12/10/2013



BLA 125504

**BLA ACKNOWLEDGEMENT**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
Building 135, Office 521  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

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

**Name of Biological Product:** COSENTYX™ (secukinumab)

**Date of Application:** October 22, 2013

**Date of Receipt:** October 24, 2013

**Our Secondary Tracking Number (STN):** BLA 125504

**Proposed Use:** Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

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/oc/datacouncil/spl.html>. 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 format and content requirements of 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 Submission Tracking 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 Dermatology and Dental Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission.

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

If you have any questions, call me at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

Matthew White  
Regulatory Health Project Manager  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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/  
-----

MATTHEW E WHITE  
12/02/2013



IND 100418

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

ATTENTION: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager

Dear Dr. Picone:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Secukinumab Injection, 150 mg/mL.

We also refer to:

- Your May 31, 2013, correspondence, received May 31, 2013, requesting review of your proposed proprietary name, Cosentyx Sensoready Pen.
- Your June 07, 2013, Proprietary Name amendment received June 07, 2013, clarifying the full proposed proprietary name for presentation of Secukinumab with the autoinjector device.

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

A request for proprietary name review for Cosentyx Sensoready Pen should be submitted once the BLA is submitted.

If **any** of the proposed product characteristics as stated in your May 31, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Matthew White, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, 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

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

/s/  
-----

CAROL A HOLQUIST  
09/16/2013



IND 100418

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation  
One Health Plaza  
East Hanover, NJ 07936-1080

ATTENTION: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager

Dear Dr. Picone:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Secukinumab for Injection, 150 mg and Secukinumab Injection, 150 mg/mL.

We also refer to your March 22, 2013, correspondence, received March 22, 2013, requesting review of your proposed proprietary name, Cosentyx. We have completed our review of the proposed proprietary name, Cosentyx and have concluded that it is acceptable.

A request for proprietary name review for Cosentyx should be submitted once the BLA is submitted. If **any** of the proposed product characteristics as stated in your March 22, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Matthew White, Regulatory Project Manager in the Office of New Drugs (OND), at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, 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

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

/s/  
-----

CAROL A HOLQUIST  
09/16/2013



IND 100418

**MEETING MINUTES**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
One Health Plaza  
East Hanover, NJ 07936

Dear Dr. Picone:

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

We also refer to the meeting between representatives of your firm and the FDA on July 24, 2013. The purpose of the meeting was to discuss the content and format of the proposed BLA.

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 Matthew White, Regulatory Project Manager at (301) 796-3935.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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:** Type B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** July 24, 2013; 9:00 a.m.  
**Meeting Location:** FDA W.O. Bldg. 22/ room 1309

**Application Number:** IND 100418  
**Product Name:** (secukinumab) Lyophilized Powder, Prefilled Syringe and Autoinjector  
**Proposed Indication:** Treatment of moderate to severe chronic plaque-type psoriasis in adult patients who are candidates for systemic therapy or phototherapy

**Sponsor Name:** Novartis Pharmaceuticals Corporation

**Meeting Chair:** Stanka Kukich, M.D.  
**Meeting Recorder:** Paul Phillips

**FDA ATTENDEES**

Julie Beitz, M.D., Director, ODE III  
Victoria Kusiak, M.D., Deputy Director, ODE III  
Maria R. Walsh, R.N., M.S., Associate Director for Regulatory Affairs, ODE III  
Stanka Kukich, M.D., Deputy Director, DDDP  
Tatiana Oussova, M.D., M.P.H., Deputy Director for Safety, DDDP  
David Kettl, M.D., Clinical Team Leader, DDDP  
Amy Woitach, D.O., M.S., Clinical Reviewer, DDDP  
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP  
Jill Merrill, Ph.D., Pharmacology Reviewer, DDDP  
Sarah Kennett, Ph.D., Review Chief, DMA  
Rashmi Rawat, Ph.D., Acting Team Leader, DMA  
Carla Lankford, M.D., Ph.D., Science Policy Analyst, TBBT  
Mohamed Alish, Ph.D., Biostatistics Team Leader, DB III  
Carin Kim, Ph.D., Biostatistics Reviewer, DB III  
Yow-Ming Wang, Ph.D., Clinical Pharmacology Team Leader, DCP3  
Jie Wang, Ph.D., Clinical Pharmacology Reviewer, DCP 3  
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP  
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP  
Jay Sitlani, J.D., M.S., Acting Division Director, DRP I, ORP  
Carlos Mena-Grillasca, R.Ph., Safety Evaluator, DMEPA

Jessica Weintraub, Pharm.D., Safety Evaluator, DPV I  
Douglas Warfield, Operations Research Analyst, OBI

### **SPONSOR ATTENDEES**

John Hohneker, Development Franchise Head, Integrated Hospital Care  
George Vratsanos, Executive Global Program Head  
Josemaria Gimenez Arnau, Senior Global Program Head  
Charis Papavassilis, Global Program Medical Director  
Simon Cooper, Global Program Medical Director  
Achim Guettner, Senior Principal Statistical Scientist  
Marianne Soergel, Senior Brand Safety Leader  
Andreas Balzer, Technical Project Leader  
Nancy Landzert, Global Regulatory CMC  
Beate Vogel, Preclinical Safety Assessment Expert  
Gerard Bruin, Drug Metabolism and Pharmacokinetics, Senior Investigator II  
Judit Nyirady, US Executive Medical Director  
Penelope Giles, Global Head, Drug Regulatory Affairs, Integrated Hospital Care  
David A D Jones, Senior Global Program Regulatory Director  
Michelle Pernice, Drug Regulatory Affairs PharmD Fellow  
Gretchen Trout, Head of North American Policy and FDA Liaison  
Katie Picone, Senior Global Program Regulatory Manager

### **Purpose of the Meeting:**

To discuss the content and format of the proposed BLA

### **Regulatory Correspondence History**

We have had the following meeting(s)/teleconference(s) with you:

- 5/27/09: Guidance meeting
- 7/15/09: Guidance meeting
- 3/2/11: Guidance meeting
- 4/17/13: Guidance meeting

We have sent the following correspondences:

- 3/27/07: Advice
- 7/7/08: Advice letter
- 11/28/08: Advice letter
- 3/13/09: Information request letter
- 7/6/09: Information request letter
- 10/1/09: Advice letter
- 1/12/10: Information request letter
- 3/17/10: Advice letter
- 5/19/10: Information request letter
- 6/3/11: Pre-meeting communication

- 7/12/11: Advice/information request letter
- 9/9/11: Advice/information request letter
- 12/12/11: Advice letter
- 1/6/12: Information Request
- 7/6/12: Advice/information request letter (2)
- 7/9/12: Advice letter (2)
- 7/11/12: Advice letter
- 10/15/12: Advice letter
- 11/1/12: Advice letter (2)
- 11/15/12: Advice letter
- 11/27/12: Advice letter
- 3/21/13: Combined annual report granted letter
- 3/28/13: Inadequate study request letter
- 4/5/13: Advice letter
- 4/18/13: Advice letter
- 7/31/13: Advice letter

**Meeting Discussion:**

The FDA inquired if the application will be complete upon submission. The sponsor stated they do not plan to provide any component of the application after the original BLA submission.

**Chemistry, Manufacturing and Controls (CMC)**

**Question 4:**

Does FDA agree that a sufficient stability package is available to support the proposed shelf-life of the lyophilisate in vial, pre-filled syringe and autoinjector/pen formulation?

**Response:**

Based on the information in the meeting package, your proposal to request a 36 months shelf life for the 150 mg Lyophilisate in vial based on the 36 months stability data at the long term storage condition of 2-8°C from three lots manufactured using commercial manufacturing process appears reasonable. A final decision on the acceptability of the data to support the proposed shelf-life will be a BLA review issue.

Based on the information in the meeting package, it is unclear that a 24 month shelf life for pre-filled syringe (PFS) and autoinjector (AI) would be granted based on the supporting stability data from the developmental bulk syringe batches. Under certain circumstances it may be appropriate to use stability data from clinical trial batches as the primary stability data set for setting commercial expiry dating. However, we have experience with other products where stability data from process validation lots were not consistent with those from clinical trial lots, even in the absence of significant manufacturing changes, and the reasons for the inconsistencies could not be easily identified. We consider a number of factors when weighing the reliability of stability data from clinical lots to support commercial expiry. These include such things as the nature of any process changes introduced prior to conducting process validation, the adequacy of the

stability protocols, the strength of the analytical methods, including the range of product attributes covered, the demonstrated stability-indicating potential of the methods, the actual results of the stability studies, including whether the data are sufficiently comparable.

In addition, the BLA will need to include a justification that the additional manufacturing steps that are part of the manufacturing process of the PFS and the autoinjector do not impact their stability profile compare to the bulk PFS. These justification studies should include the stability data from the PFS and AI pen batches that were manufactured under worst case conditions for temperature and production time. In addition, the BLA should include data that demonstrates that the rate and degradation pathways for the bulk-PFS, PFS and AI are comparable.

**Meeting Discussion:**

The sponsor asked the FDA to clarify the CMC response for the use of 24 month stability data from clinical lots to support the shelf life of pre-filled syringe and autoinjector. The FDA clarified that we need supporting data besides the 24 month stability data from the clinical lot, and the supporting data should include any process change introduced prior to conducting process validation, adequacy of stability protocol and analytical method to be used. The FDA also requested that the sponsor submit the comparison of the rate and pathways of degradation between the clinical lots and the process validation lots. The sponsor acknowledged our feedback and agreed they will submit these data.

The FDA indicated if additional stability data are needed to support the requested expiry dating we will request this through an information request during the review period.

**Question 5:**

Pre-filled syringe with safety device and autoinjector/pen presentations of secukinumab are combination products with drug and device components. Novartis plans to submit the device information for PFS (b)(4) and AI in the drug product modules of the BLA (e.g., P2 and P7). Novartis requests that CDER and CDRH collaboratively review this application in parallel. Does the FDA agree with this approach?

**Response:**

CDRH will provide a collaborative real-time review of the device data submitted to the BLA. Your initial proposal to provide the 510 K summary for the (b)(4) device, letters of authorization for the (b)(4) Syringe, barrel and plunger stopper, and the (w)(4) pen injector master files will be an acceptable method for demonstrating performance parameters of the devices. Note, however, that for syringes with sharps injury protection features CDRH expects simulated clinical testing to demonstrate safety and efficacy. In addition, CDRH will require a Human Factors Usability Study to demonstrate that the pen injector can be used by the target population (patients, caregivers, clinicians) without patterns of use failure. Refer to FDA Guidance for Industry and FDA Staff Medical Devices with Sharps Injury Prevention Features, August 2005 and Draft Guidance for Industry and Food and Drug Administration Staff - Applying Human Factors and Usability Engineering to Optimize Medical Device Design.

**Pharmacology/Toxicology**

There are no additional nonclinical studies required to support a BLA submission for secukinumab. However, we remind you of the requirement to assess and address the potential carcinogenic risk associated with secukinumab (AIN457) in the BLA submission. The following comments were previously relayed to you in an Advice/Information Request Letter on March 17, 2010.

*While we agree that no additional nonclinical studies are needed to address the carcinogenic potential of AIN457, the immunosuppressive properties of AIN457 will need to be adequately addressed in the label. Pharmacovigilance alone may not be adequate to address the issue of carcinogenicity. This will remain a review issue likely to be addressed upon BLA submission.*

*We acknowledge that you have submitted a literature summary to the IND. However, you should provide the literature references addressing the effects of IL-17a inhibition and potential carcinogenic risk. This information will be needed for labeling purposes. The published literature could provide information from transgenic, knock-out, animal disease models or human genetic diseases to assist with understanding the potential carcinogenic risk associated with AIN457.*

A BLA submitted under section 351(a) of the PHS Act must contain all required data and information necessary to demonstrate the safety, purity, and potency of the proposed biological product. A BLA submitted under section 351(a) of the PHS Act is a “stand-alone” application and may not rely on product-specific published literature describing studies of other biological products, including studies regarding a licensed biological product, to fulfill a requirement for licensure. You may however rely on generally accepted scientific knowledge regarding the effects of IL-17a inhibition and potential carcinogenic risk. This may include relevant data and information (including non product-specific published literature) that generally explains the effects, effects of IL-17a inhibition and potential carcinogenic risk.

## **Clinical**

### **Question 1:**

Does FDA agree that the clinical package for secukinumab including the recent phase 3 efficacy & safety data from studies CAIN457A2302, CAIN457A2308 & CAIN457A2304 appears to be a sufficient basis/profile for submission for the proposed indication?

### **Response:**

You propose to include in your BLA submission complete study report data for Phase 3 studies CAIN457A2302, CAIN457A2303, CAIN457A2304 (52 weeks); CAIN457A2308, CAIN457A2309 (12 weeks). The clinical program you have outlined in your briefing package would likely be found acceptable for filing of your BLA.

### **Meeting Discussion:**

The sponsor acknowledged that they plan to submit complete study reports from the studies listed in the FDA response above.

The sponsor stated that they plan to propose a secukinumab dose of 300 mg.

**Question 2:**

Does FDA agree with the proposed potential risks for risk management planning?

**Response:**

It is unlikely that a REMS will be required for the safe use of secukinumab as a treatment of psoriasis based on our review of the summarized information contained in your meeting package. However, the final determination for necessity of a REMS depends on the overall risk benefit assessment of your application and will be decided after your complete application has been reviewed.

A complete review of the full risk management plan after the BLA is submitted will be necessary to determine whether the proposed approach is acceptable, since additional information regarding risks and safe product use may emerge during the review of your BLA.

**Meeting Discussion:**

The sponsor proposed to submit the REMS proposal with their application. The FDA stated that a final determination regarding whether or not a REMS is necessary would be made during the course of the BLA review cycle.

**Question 3a:**

Does FDA agree that sufficient data will be provided at time of BLA submission to support the bio-comparability of EU-sourced Enbrel utilized in study CAIN457A2303 to US-sourced Enbrel?

**Response:**

It is not clear what you mean by supporting the “bio-comparability” of EU-approved etanercept and US-licensed Enbrel. It is also not clear what the intent is of a demonstration of “bio-comparability” of EU-approved etanercept and US-licensed Enbrel in relation to your intended initial BLA submission to seek approval of secukinumab. While Study CAIN457A2303 was designed as a 3-arm study, the determination that secukinumab is safe and efficacious is based on the demonstration that secukinumab is superior to placebo.

If by “bio-comparability” you intended to refer to a demonstration of similarity, a demonstration of pharmacokinetic (PK) similarity between EU-approved etanercept and US-licensed Enbrel would not, by itself, be sufficient to establish similarity. Comparative analytical (structural and functional) characterization data in addition to PK similarity data would generally be required to establish a bridge between EU-approved etanercept and US-licensed Enbrel to justify the relevance of data obtained using EU-approved etanercept.

(b) (4)

**Meeting Discussion:**

The sponsor proposed to apply concepts for the demonstration of biosimilarity from existing FDA draft guidances regarding biosimilarity (b) (4)

(b) (4)

(b) (4)

(b) (4)

**Question 3b:**

(b) (4)

**Response:**

(b) (4)

(b) (4)

**Question 3c:**

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

**Regulatory:**

**Question 6:**

Does FDA agree with the proposal for the submission of financial disclosure?

**Response:**

Financial disclosure information should be submitted for all clinical investigators who conducted clinical studies for which you intend to rely on to establish that secukinumab is effective and any study in which a single investigator makes a significant contribution to the demonstration of safety. Refer to the updated guidance for clinical investigators, industry, and FDA staff *Financial Disclosure by Clinical Investigators* (February 2013).

Your proposal for covered clinical studies regarding secukinumab appears to be consistent with the Agency's requirement.

**Question 7:**

Does FDA agree with the proposed format and outline of the eCTD (TOC provided in Appendix 2) is adequate for filing this submission?

**Response:**

From a technical standpoint (not content related) yes, the proposed format and outline is adequate for filing this submission, however, see additional comments below:

- Providing Table of Contents in 2.1 and 4.1 is not necessary in the eCTD structure. Instead, provide a linked reviewer's aid/ reviewer's guide for an original application in module 1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application.

- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 (tabular format), should be linked to the referenced studies in m5.
- Providing one 3.2.S and one 3.2.P Manufacturing section with attribute of "ALL" and differentiating documents by leaf title is acceptable. Additionally, indicating the substance/product name at the beginning of leaf titles, helps sorting abilities when sorting by substance or product.
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at:  
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>.
- Regarding use of the m5-3-7 heading element, we do not use module 5.3.7 CRFs. Instead, case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as "case report form" and reside with the study's information. Do not use 5.3.7 as a heading element in the index.xml
- To submit PADER\PSUR descriptive portion in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in the eCTD section, m5.3.6. Ensure that the leaf title of the report includes the reporting period, since each report is for a specific time period and it also helps when the leaf title follows a standard format, so reviewers can quickly differentiate one years' report, from another

**Question 8:**

Does FDA agree with the proposed content of the 120 day safety update?

**Response:**

For the 120 day safety update submission, you propose a 3 month cut-off date from the date of BLA submission. As long-term trials will be ongoing and continue to generate safety data, we recommend you choose a cut-off date of at least 3 months if not longer. Additionally, 7-day and 15-day safety reports should continue to be submitted to the IND for all ongoing secukinumab studies.

**Meeting Discussion:**

The sponsor committed to send the most up-to-date safety information.

### **Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or BLA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, refer to 21CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. Request a submission tracking number (STN) assignment prior to the submission of your BLA.
5. You should provide the Agency with SAS transport files in electronic form. The sponsor might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance: [http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam\\_examples\\_final.pdf](http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf). The FDA prefers that the sponsor arrange a test submission, prior to actual submission. Refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov), or for standardized data submission questions, contact [edata@fda.hhs.gov](mailto:edata@fda.hhs.gov).

### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that at this time the FDA did not think a REMS was likely to be required. The sponsor nevertheless asked if they could submit a REMS in case the FDA determined during the course of the review of the BLA that a REMS would be required. The FDA agreed that

the sponsor could submit a REMS and a final determination regarding whether or not a REMS is necessary would be made during the course of the BLA review cycle.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

### **PREA REQUIREMENTS**

We note that you plan to submit per FDAAA.

### **PRESCRIBING INFORMATION**

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[*see Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

### **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, NDA/BLA 012345, Establishment Information for Form 356h."

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

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

## Attachment 1

### **CLINICAL INVESTIGATOR SITE INFORMATION**

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 major trials used to support safety and efficacy in the application (i.e. phase 2/3 pivotal trials). 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 (see 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).**

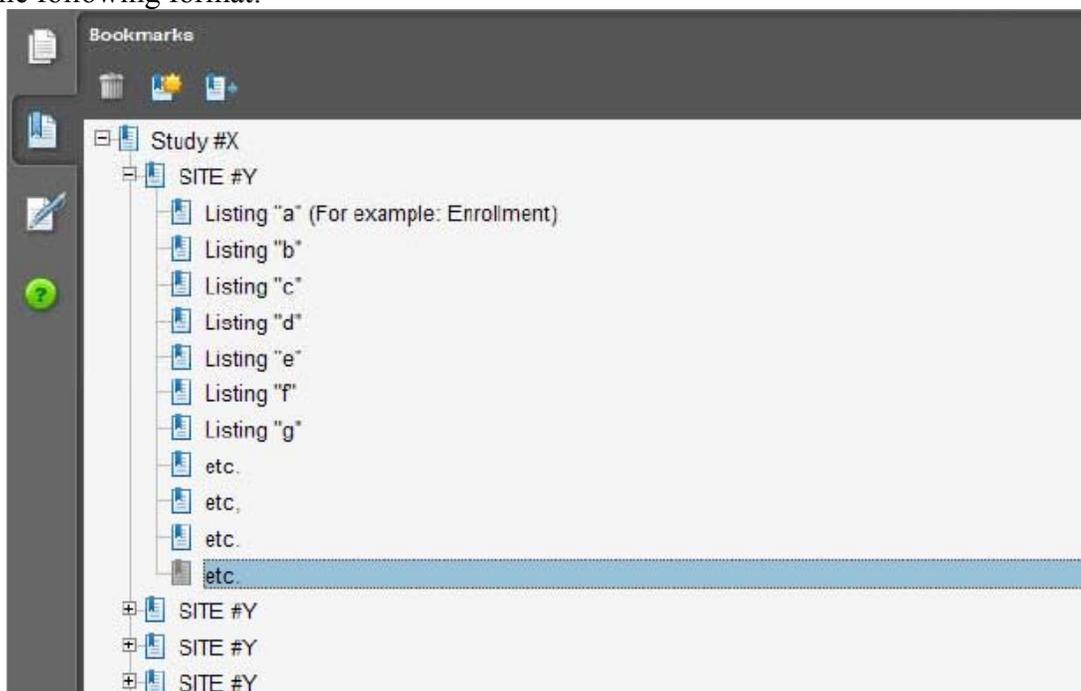
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - 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 original NDA for each of the completed pivotal clinical trials:
  - 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 NDA for each of the completed pivotal clinical trials:

- 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 pivotal trial, 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 pivotal trial 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 pivotal trial: 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 NDA, 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 pivotal clinical trials)
  - 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 pivotal Phase 2 and Phase 3 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.

## 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 Item <sup>1</sup>	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

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

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](mailto:ESUB@fda.hhs.gov)

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

/s/  
-----

STANKA KUKICH  
08/22/2013



IND 100418

**MEETING MINUTES**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Sr. Global Program Regulatory Manager  
Integrated Hospital Care  
One Health Plaza  
East Hanover, New Jersey 07936-1080

Dear Dr. Picone:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AIN457 (secukinumab).

We also refer to the teleconference between representatives of your firm and the FDA on April 17, 2013. The purpose of the meeting was to discuss the development program for (secukinumab).

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

If you have any questions, call Matthew White, Regulatory Project Manager at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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:** C  
**Meeting Category:** Guidance

**Meeting Date and Time:** April 17, 2013 at 9:00 a.m.  
**Meeting Location:** Teleconference

**Application Number:** IND 100418  
**Product Name:** AIN457 (secukinumab) Lyophilized Powder, Prefilled Syringe, and Autoinjector

**Proposed Indication:** Treatment of moderate to severe chronic plaque-type psoriasis in adult patients who are candidates for systemic therapy or phototherapy

**Sponsor Name:** Novartis Pharmaceuticals Corporation

**Meeting Chair:** Stanka Kukich, M.D.  
**Meeting Recorder:** Matthew White

**FDA ATTENDEES**

Stanka Kukich, MD, Deputy Director, DDDP  
David Kettl, MD, Clinical Team Leader, DDDP  
Amy Woitach, DO, MS, Clinical Reviewer, DDDP  
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III  
Carin Kim, PhD, Biostatistics Reviewer, DB III  
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3  
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3  
Barbara Rellahan, MS, PhD, Product Quality Team Leader, DMA  
Rashmi Rawat, PhD, Product Quality Reviewer, DMA  
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP  
Matthew E. White, Regulatory Health Project Manager, DDDP

**SPONSOR ATTENDEES**

Jose Maria Gimenez Arnau, Global Program Head  
Simon Cooper, Global Program Medical Director  
Charis Papavassilis, Global Program Medical Director  
Marianne Soergel, Brand Safety Leader  
Achim Guettner, Statistical Scientist  
Peter Mesenbrink, Statistical Scientist  
Nancy Landzert, Global Regulatory CMC

Andreas Balzer, Technical Project Leader  
Penny Giles, Global Regulatory Franchise Head  
David Jones, Global Program Regulatory Director  
Florent Hartmann, Global Program Regulatory Manager  
Katie Picone, Global Program Regulator Manager

**Purpose of the Meeting:**

The purpose of the meeting is to discuss the development program for AIN457 (secukinumab).

**Regulatory Correspondence History**

We have had the following meeting(s)/teleconference(s) with you:

- 4/27/09: Guidance meeting
- 7/15/09: Guidance meeting
- 3/2/2011: Guidance meeting

We have sent the following correspondences:

- 3/27/07: Advice
- 7/7/08: Advice letter
- 11/28/08: Advice letter
- 3/13/09: Information request letter
- 7/6/09: Information request letter
- 10/1/09: Advice letter
- 1/12/10: Information request letter
- 3/17/10: Advice letter
- 5/19/10: Information request letter
- 6/3/11: Premeeting communication
- 7/12/11: Advice/information request letter
- 9/9/11: Advice/information request letter
- 12/12/11: Advice letter
- 1/6/12: Information Request
- 7/6/12: Advice/information request letter (2)
- 7/9/12: Advice letter (2)
- 7/11/12: Advice letter
- 7/23/12: Information request letter (electronic)
- 8/16/12: Information request letter (electronic)
- 10/15/12: Advice letter
- 11/1/12: Advice letter (2)
- 11/15/12: Advice letter
- 11/27/12: Advice letter

### **Chemistry, Manufacturing and Controls (CMC)**

1. The briefing package indicates that you plan to perform release testing of (b) (4). We recommend that your justification for this approach include a risk assessment of the potential for time, temperature and handling conditions encountered during the autoinjector assembly process to impact product quality. In addition, 21 CFR 610.14 states that an identity test must be performed on products after all labeling operations have been completed. If labeling occurs after assembly of the autoinjector, identity testing will need to be performed on each autoinjector lot.
2. We note that the lyophilized vial presentation still includes a (b) (4) % overfill volume which exceeds USP <1151> recommendations. It is recommended that the overfill volume be reduced to conform to USP recommendations. If the overfill volume is not reduced, the BLA should include a robust justification for exceeding the USP <1151> recommendations.

#### **Meeting Discussion:**

The Agency clarified that the identity test is the analytical identity release test performed on the product after final labeling of the DP container has been performed. If the final labels are placed on the prefilled syringes prior to packaging in the autoinjector then identity testing performed on the bulk PFS lot is acceptable. However if the final labeling of the product is done after autoinjector assembly, then identity testing should be performed on each autoinjector lot.

In regard to the overfill volume, the sponsor agreed to provide justification for exceeding USP recommendations in the BLA. The Agency clarified that the justification should include information on the accuracy of the filling line to support use of overfill volumes that exceed USP <1151> recommendations.

3. It was noted that many of the acceptance criteria outlined in Table 5-3 of Appendix 1 fall significantly outside of the ranges reported in the representative results. For licensure, acceptance criteria, including those for particulate matter, should be based on your pre-clinical and clinical experience.

### **Clinical/Clinical Pharmacology/Biostatistics**

No preliminary Phase 3 safety and efficacy information has been provided in the briefing document, and Phase 3 studies are ongoing and still blinded. Detailed comments on the content and format of your complete application and Agency agreements will be provided at a pre-BLA meeting.

Our responses are based on the information you have submitted from your Phase 2 studies:

**Question 1:**

Does FDA agree with the proposed pooling strategy and sub-group analyses planned for the future submission package specifically within the Summary of Clinical Efficacy (SCE; CTD module 2.7.3)?

**Response:**

You stated that while you plan to provide individual efficacy data for each clinical trial in the Clinical Study Reports (Module 5), you propose to pool data from Phase 3 trials to create two different pooled databases for efficacy in order to evaluate the short-term efficacy (12 week) as well as long-term efficacy of secukinumab using meta-analysis for Module 2.7.3. Furthermore, you plan to conduct subgroup analyses on co-primary and secondary endpoints, and listed several subgroup variables. While you might conduct pooled efficacy analyses as well as subgroup analyses as exploratory analyses, it should be noted that establishing an efficacy claim would be based on efficacy data from individual Phase 3 trials that provide replication of study findings.

You propose, in lieu of an Integrated Summary of Efficacy (ISE), to provide a Summary of Clinical Efficacy (module 2) with an integrated analysis of efficacy in the SEC appendix (module 5). In addition to the subgroup analyses you propose, your integrated analyses should discuss the effectiveness of the drug across the studies and comment on the consistency of study findings.

**Question 2:**

Does FDA agree with the proposed pooling strategy and sub-group analyses planned for the future submission package specifically within the Summary of Clinical Safety (SCS; CTD module 2.7.4)?

**Response:**

You propose, in lieu of an Integrated Summary of Safety (ISS), to provide a Summary of Clinical Safety (module 2) with an integrated analysis of safety data in the SCS appendix (module 5).

Your proposed pooling strategy of three pooled databases (psoriasis placebo-controlled Phase 3 studies, psoriasis Phase 2/3 studies, all secukinumab studies) for safety analysis seems reasonable. However, we will need an understanding of the effect of prolonged use on the safety profile of this product and you should include duration of use in your pooling strategy.

In addition to the information required in the ISS, provide the following to aid our review:

1. Shift tables for all laboratory values for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

**Meeting Discussion:**

The sponsor stated that they consider a CTC grade 3 change to be clinically significant. The Agency stated that, for a psoriasis indication, the risk/benefit would be better informed by including data for a grade 2 change as clinically significant.

2. A summary of reported adverse events for autoimmune diseases. Include both systemic (e.g. lupus, vasculitis, sarcoidosis, antiphospholipid syndrome and inflammatory myopathies) and organ-specific (e.g. interstitial lung disease, uveitis, optic neuritis, peripheral neuropathies, multiple sclerosis, psoriasis, inflammatory bowel disease and autoimmune hepatitis) autoimmune processes.

**Question 3:**

Does FDA agree with the proposed definition of MACE events?

**Response:**

There are both broad and narrow search terms under standardize MedDRA queries. We recommend that you use both to analyze MACE events. Relevant events not captured in your query include heart failure, arrhythmia, unstable angina, transient ischemic attack, venous thrombotic events (DVT/PE), and peripheral arterial thrombosis.

**Question 4:**

Does FDA agree with the proposed approach to assess the potential risk for infections?

**Response:**

Although limited information from the Phase 2 studies has been provided, the proposed approach seems reasonable. Additional information may be requested during the BLA review.

**Question 5:**

Does FDA agree with our proposed provision of patient narratives and CRFs?

**Response:**

The following data should be included:

- Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation from the trials conducted with your product.
- The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

**Meeting Discussion:**

The sponsor inquired whether the date of enrollment is the date of signing of the informed consent form. The Agency clarified that the date of enrollment is intended to be the date of randomization.

- Case report forms (CRFs) for all serious AEs, all severe AEs, and for all subjects who discontinued from the studies for any reason. A study's CRFs should be placed in a CRF folder under the applicable study with a file tag of "case-report-forms." Also provide the following:

Electronic links for:

- a. all serious AEs
- b. all severe AEs
- c. all patients discontinued regardless of reason
- d. all deaths

CRFs should be referenced under the study in which it belongs and tagged as "case-report-forms" in that study's stf.xml file. CRFs that are not submitted should be readily available upon request.

- Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality)  $\geq 1\%$ .
- Adverse event tables  $\geq 1\%$  regardless of causality.
- Line listings for all safety data.

**Question 6:**

Does FDA agree with our proposed formats of datasets, in particular on the CDISC compliant structure of SDTM and ADaM datasets, as well as case report tabulations data definition specification (CRT-DDS)?

**Response:**

Your proposal to submit SDTM, ADaM datasets and to utilize CRT-DDS standard are acceptable. For individual datasets, you should provide the Agency with SAS transport files in electronic form. The submission should include adequate documentation for the data sets including definitions of each variable in the data set, formulas for derived variables and decodes for any factor variables so that all categories are well-defined in the documentation. The documentation should indicate which variables are derived.

In addition to the electronic data sets, the submission should include the following items for the Phase 3 trials:

1. Study protocols including the statistical analysis plan, protocol amendments and their dates, and an annotated copy of the Case Report Form.
2. The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.

3. For the analysis dataset, the sponsor should include the treatment assignments, outcomes for each scheduled visits along with variables that indicate the original study site as well as the analysis study site.

For submission of biopharmaceutics analysis data sets, we remind you the following:

- Submit NONMEM control streams of the base and final model for population PK analysis.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt). Submit a model development decision tree and/or table which gives an overview of modeling steps.
- In data sets for pharmacokinetic (PK), pharmacodynamic (PD), and exposure-response relationship analysis, any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Separately the reasons for subject removal should be provided for each subject in a separate file linked to their individual case report form.
- All analysis datasets used in non-model-based analysis should be submitted in the xpt format.

We prefer that you arrange a test submission prior to actual submission. Refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov), or for standardized data submission questions, contact [edata@fda.hhs.gov](mailto:edata@fda.hhs.gov).

### **Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the IND might identify additional comments or information requests.
2. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.

3. Your Pre-BLA meeting for AIN457 (secukinumab) is scheduled for July 24, 2013 at 9:00 a.m.

### **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

/s/  
-----

STANKA KUKICH  
05/13/2013



IND 100418

**MEETING MINUTES**

Novartis Pharmaceuticals Corporation  
Attention: Shilpa Kurpad, Pharm.D.  
Global Program Regulatory Manager  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Kurpad:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for secukinumab (AIN457).

We also refer to the meeting between representatives of your firm and the FDA on March 2, 2011. The purpose of the meeting was to discuss the development program for secukinumab.

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

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
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:** Type B  
**Meeting Category:** Guidance

**Meeting Date and Time:** March 2, 2011; 10:30 a.m. (EDT)  
**Meeting Location:** FDA W.O. Bldg. 22, room 1311

**Application Number:** IND 100418  
**Product Name:** secukinumab (AIN457)  
**Proposed Indication:** Treatment of moderate to severe chronic plaque-type psoriasis in adult patients who are candidates for systemic therapy or phototherapy

**Sponsor/Applicant Name:** Novartis Pharmaceuticals Corporation

**Meeting Chair:** Susan J. Walker, M.D.  
**Meeting Recorder:** Paul Phillips

**FDA ATTENDEES**

Susan J. Walker, M.D., F.A.A.D., Director, DDDP  
David Kettl, M.D., Clinical Team Leader, DDDP  
Amy Woitach, D.O., Clinical Reviewer, DDDP  
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP  
Carmen Booker, Ph.D., Pharmacology Reviewer, DDDP  
Barbara Rellahan, M.S., Ph.D., Product Quality Team Leader, DMA  
Rashmi Rawat, Ph.D., Product Quality Reviewer, DMA  
Lanyan (Lucy) Fang, Ph.D., Clinical Pharmacology Reviewer, DCP3  
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DB III  
Carin Kim, Ph.D., Biostatistics Reviewer, DB III  
Elektra Papadopoulou, M.D., Medical Officer, SEALD  
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP  
Kimberly Shiley, R.N., B.S.N., B.S.B.A., Regulatory Health Project Manager, DDDP  
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

**SPONSOR ATTENDEES**

Christian Antoni, MD, PhD - Vice President, Global Program Head for Secukinumab  
Charis Papavassilis, MD, PhD - Global Program Medical Director  
Judit Nyirady, MD, MBA - US Executive Medical Director, Dermatology

Achim Guettner, PhD - Program Statistician  
Oliver Sander, PhD - Modeling and Simulation Statistics, Senior Modeler  
Michael Looby, PhD - Modeling and Simulation - Translational Modeler  
Gerardus Bruin, PhD - Global PK/PD Senior Investigator II  
Beate Vogel, PhD - Preclinical Safety Assessment Expert  
Edward Kim, MD, MBA - Health Economics and Outcomes Research, Therapeutic Area Head  
Agata Slopianka, PhD - Global Regulatory CMC Project Team Leader  
Penelope Giles, PhD - Global Head, Drug Regulatory Affairs-Integrated Hospital Care  
David AD Jones - Global Program Regulatory Director for Secukinumab  
Chin Koerner - Drug Regulatory Affairs  
Shilpa Kurpad, PharmD - Global Program Regulatory Manager

### **Regulatory Correspondence History**

We have had the following meetings with you:

- 4/27/09: Guidance meeting
- 7/15/09: Guidance meeting

We have sent the following correspondences:

- 3/27/07: Advice
- 7/7/08: Advice letter
- 11/28/08: Advice letter
- 3/13/09: Information request letter
- 7/6/09: Information request letter
- 10/1/09: Advice letter
- 1/12/10: Information request letter
- 3/17/10: Advice letter
- 5/19/10: Information request letter

### **Preliminary Agency Comments:**

This meeting was granted as a Guidance meeting as your Phase 2 program is still ongoing. At this time you have completed only three single dose, I.V. studies evaluating less than 100 subjects with psoriasis. For the ongoing Phase 2 studies, safety data remains blinded; however, in study 2212 there appears to be a trend for an increased rate of infection in the treatment arm. You are referred to the meeting minutes from May 27, 2009 regarding Agency advice for dose selection for the initial, maintenance, and withdrawal/retreatment aspects of your development plan.

The Agency comments in this document provide additional guidance for your product's development. Your Phase 2 studies are ongoing and Phase 3 commitments will not be provided at this meeting.

You should request and attend an End-of-Phase 2 meeting when your Phase 2 program is complete and study results are available.

The Agency has altered the sequence of your questions to present our responses to your product quality development issues, as these will need to be considered prior to conduct of your later phase trials.

**Meeting Discussion:**

**The sponsor indicated their intention to start their Phase 3 studies in May 2011.**

**The sponsor plans to submit information to support the use of Enbrel<sup>®</sup> sourced from the U.K., including information on the manufacturing facility. The sponsor also plans submit two finalized Phase 3 protocols.**

**Question 12:**

Novartis intends to conduct a pharmacokinetics (PK) comparability study in healthy volunteers to bridge from the lyophilisate to liquid formulation for the pre-filled syringe. Is this considered an appropriate bridging approach?

**Response:**

No. we do not agree. Requirements for transitioning from a vial to a pre-filled syringe format are under discussion by the Agency. While demonstration of analytical and immunogenicity comparability, and PK comparability of the PFS format to the lyophilized format may be sufficient to support licensure, additional clinical studies may be required. It is therefore recommended that the pivotal trial(s) be conducted with the intended commercial product presentation.

**Question 13:**

Novartis intends to assess the patient-administered pre-filled syringe in at least one of the extension studies of the phase III program for psoriasis (currently proposed to be long-term extensions of CAIN457A2302, CAIN457A2303, CAIN4572304, and CAIN457A2307). Will the study as designed be sufficient to justify self-administration of this formulation in labeling at time of first approval?

**Response:**

We do not believe that the current protocol addresses comparative immunogenicity of the dosage forms. We recommend that you collect PK samples and address immunogenicity of the two dosage forms.

**Meeting Discussion:**

**In the proposed extension study, patients would receive both dosage forms sequentially. Immunogenicity assessments should include subjects who have only received one of the proposed dosage forms. The sponsor should propose a sample size with supporting rationale to justify these assessments.**

You should assess the safety and effectiveness of the glass syringe that is utilized as the device constituent of your combination product. The syringe appears to be a single use, glass barrel, hypodermic syringe with a rigid needle shield. You should strongly consider the recommendations stated with the following ISO Standards:

ISO 11040-4, regarding glass barrels for syringes  
ISO 7864-1, regarding sterile, hypodermic needles for single use

CDRH utilizes the recommendations stated within these ISO Standards when assessing the safety and effectiveness of a glass barrel syringe with a staked needle.

Regarding biocompatibility, CDRH relies on the ISO Standard, ISO 10993, *Biological Evaluation of Medical Devices*. We are aware that CDER has asked a comprehensive set of questions regarding the safety of your drug, and assessment of the leachables / extractables. You should consider the requirements in ISO 10993 for demonstrating the biocompatibility aspects of the syringe. Of course, if there is overlap between ISO 10993 and the standards / guidance that CDER typically refers to, then you may consolidate your testing.

Additionally, your device contains a rigid needle shield. FDA has issued a guidance regarding the testing of needle stick prevention devices. The Guidance states that you should perform 500 activations of your needle stick prevention mechanism and demonstrate that there are zero (0) failures of the mechanism within these 500 activations. This demonstrates that you have achieved a 99% confidence interval in demonstrating the safety and effectiveness of the rigid needle shield. The Guidance, titled *Medical Devices with Sharps Injury Prevention Features*, is located on FDA's website at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071755.pdf>.

Furthermore, it appears that the syringe appears will be utilized by the lay person for self-administration of AIN-457 / secukinumab. You should assess the use-related risks associated with the lay person utilizing the device. You should perform a comprehensive human factors study to assess these use-related risks. FDA has issued a guidance document regarding human factors titled *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*. This Guidance is located on FDA's website at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm>. Please note that Sponsors often attempt to utilize clinical efficacy studies, user satisfaction / ease of use studies, and/or labeling comprehension studies as substitutes to comprehensive human factors studies. These studies, which may be necessary to demonstrate the safety and efficacy of the drug, or demonstrate some other aspect of your combination product, are not suitable substitutes of a comprehensive human factors assessment of use-related risk. Please review FDA's human factors guidance prior to developing / conducting your Human Factor study. You are encouraged to submit your Human Factor Study Protocol to the FDA for review prior to conducting your study.

**Question 14:**

Novartis intends to submit for two formulations at the time of BLA filing, a lyophilized powder in vial and a liquid in pre-filled syringe. Is the preclinical, quality, and clinical plan outlined in this briefing book considered sufficient for the registration of both of these formulations?

**Response:**

If it is determined by the Agency that appropriate comparability has been demonstrated for the lyophilized powder in vial and the liquid in pre-filled syringe, then additional nonclinical studies would not be needed. However, if adequate comparability is not demonstrated then conduct of a 13 week bridging toxicity study in monkeys may be needed.

Based on the limited CMC information provided in the submission the overall approach to demonstration of analytical comparability between the lyophilisate in vial (LyV) and pre-filled syringes (PFS) appears to be acceptable. Please note the following comments:

1. Potential leachates (e.g., (b)(4)) from the PFS should be identified and data on the level of these impurities in the PFS drug product should be provided.
2. For licensure, if (b)(4) is a potential leachate, (b)(4) spiking studies should be performed to evaluate the effect of (b)(4) on drug product (DP) quality and stability. These studies should include, but not be limited to, a concentration of (b)(4) that is an order of magnitude greater than the highest amount detected in the PFS drug product lots.
3. To support the licensure of the PFS formats, information on the concentration of (b)(4) in the liquid syringe DP will be required. This should include information from drug product lots produced using more than one syringe lot. Data to support DP quality and stability in the presence of (b)(4) should come from PFS lots which contain a 'worst case scenario' of (b)(4) leachate. A robust characterization on the consistency of (b)(4) application to syringe lots should also be provided.
4. The comparability studies between LyV and PFS drug product should include a thorough comparison of degradation pathways of product stored in each format including the rate and pathway of degradation.
5. The (b)(4)% overfill volume for the LyV formulation appears to be unusually large and is higher than that recommended by USP<1151>. At the time of licensure the overfill volume for all DP formats need to comply with USP limits as per 21CFR 201.15 (g) or a robust justification for the overfill volume, supported by data, will be required.
6. Provide a detailed description of the methodology and plans for validation of the assays that will be used for the detection of anti-drug antibodies (ADA). The qualification results should include data demonstrating that the assay is specific, sensitive and reproducible, and should include information on the sensitivity of the assay to product interference. The validated assay should be capable of sensitively detecting ADA responses in the presence of drug levels that are expected to be present at the time of patient sampling. Provide information on the expected product levels that will be present in patient samples to support use of the assay. An assay should also be developed that is able to delineate neutralizing ADA responses. Until an assay (s) has been developed and validated, patients samples should be banked under appropriate storage conditions.

Based on FDA's review of your submission, it appears that you have three distinct presentations of AIN457 / secukinumab: 1) lyophilized powder in a vial, 2) single use, liquid pre-filled syringe and 3) single use auto injector housing one pre-filled syringe.

Regarding the lyophilized powder / vial, will this presentation be co-packaged with a glass barrel syringe (presumably pre-filled with the diluent), or will it be distributed as a stand alone container / closure? You should demonstrate the safety and effectiveness of the glass barrel syringe (if it accompanies the lyophilized powder). You should also perform the appropriate Human Factors Studies to demonstrate that the use-related risks for this configuration are appropriately mitigated. Our comments in Question 13 may apply to the lyophilized powder / vial presentation depending on how it is configured.

Regarding the liquid prefilled syringe, we have already provided comments in our response to Question 13.

Regarding your auto injector, please see our response to Question 15.

**Question 15:**

Provided analytical (CMC)-comparability between the pre-filled syringe and the auto-injector is demonstrated, does the agency agree that the following assessments/studies are adequate and sufficient to support the approval of a commercial auto-injector?

- auto-injector design verification
- auto-injector manufacturing process validation
- auto-injector design validation (simulated clinical use with injection pads)
- auto-injector clinical use study (actual patient self-injection)

**Response:**

In addition to the above assessments you should conduct PK comparability.

CDRH generally agrees with your approach. However, we have provided the following additional comments to avoid any confusion due to terminology. Regarding, design verification and validation, the intent of these activities is to ultimately demonstrate that the hazards associated with the device (and especially those that pose a risk to patients) have been successfully mitigated. These activities are performed through verification (verification of dimensional, material compatibility aspects, etc.), functional bench testing (to assess the operational performance of the device), simulated use testing (Human Factors Testing), and where necessary, clinical testing.

With regard to performance testing of the auto injector, your submission correctly identified ISO 11608 as a standard for assessing auto injector. You should also be aware that FDA has a DRAFT Guidance on Auto Injectors titled *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products*. This document is located on FDA's website at:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf>.

Additionally, if the auto injector also has a needle stick prevention mechanism, you should

adhere to FDA's guidance on this mechanism (reference provided in our response to Question 13).

With regard to the Human Factors Study, your submission indicates that the auto injector may be potentially utilized by the pediatric population. It is unclear whether the pediatric population will be self-administering the drug via the pre-filled syringe configuration. Please make sure that your human factor studies incorporate the pediatric population as appropriate. FDA has issued a Guidance document specifically for medical devices used by the pediatric population titled, *Premarket Assessment of Pediatric Medical Devices*. This guidance is located on FDA's website at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm>.

**Question 7:**

The proposed phase III program will assess psoriasis signs and symptoms as reported by the patient using the Psoriasis Diary instrument developed by the Sponsor. The Psoriasis Diary was developed in ways consistent with the FDA's "Guidance for Industry, Patient Reported Outcomes: Uses in Medical Product Development to Support Labeling Claims", and with previous guidance received from the FDA regarding the importance of the patient's perspective in psoriasis in clinical trials. The Psoriasis Diary is considered capable of evaluating treatment effectiveness among patients with chronic plaque-type psoriasis. Does the Agency agree that the methods and results of the psychometric validation (see Section 3.7 and Appendix 2) support the use of the Psoriasis Diary in the phase III program?

Novartis believes the Psoriasis Diary is capable of generating PRO signs and symptoms data to be reflected in the product labeling. Does the Agency agree?

**Meeting Discussion:**

**The Agency stated that fulfilling PRO guidance criteria is not necessarily a determination of acceptability of PRO endpoints as appropriate for eventual labeling. Certain elements of the patient reported criteria may be repetitive with PASI criteria. Furthermore, multiplicity adjustments may need to be considered.**

**Response:**

The following comments are based upon review of your submission of October 1, 2010.

You have proposed removing the following items, because they did not affect a large proportion of the sample and thus were not sensitive to change:

- Item 18 (In the past 24 hours, how hard was it to bend your joints because of the psoriasis on your skin?);
- Item 19 (In the past 24 hours, how hard was it to walk because of the psoriasis on your skin?); and
- Item 20 (In the past 24 hours, how hard was it to use your hands or fingers because of the psoriasis on your skin?).

Please also consider and discuss whether revision of the wording of these items may improve their relevance to patients. For example, it is unclear whether item 18 is asking patients to rate symptoms of pain or discomfort associated with bending joints or actual impairment of bending joints due to tight skin. A concept map for each of the items will be useful for clarification of the concept targeted by each item as well as any planned future translation and cultural adaptation for use in multinational studies.

A PRO dossier submission will be needed to review the content validity and other measurement properties of the final 16-item Psoriasis Diary in accordance with the 2009 PRO Guidance for Industry. The current submission contains the final report of the validation study, but does not include a copy of the final instrument and other important elements for Agency review including the following:

1. The a priori statistical analysis plan for the assessment of the Psoriasis Diary measurement properties;
2. A scoring algorithm for the instrument that clarifies whether or not you propose an overall summary score for the instrument;
3. The copy of the final instrument as it will be administered to patients in planned phase 3 clinical studies;
4. The revised conceptual framework for the instrument;
5. Any revisions to the targeted labeling claims;
6. The item-tracking matrix explaining the history of item development including items added, items removed and items modified with rationale these changes; and
7. A comparison of the baseline disease characteristics of the patient population in the phase 2 study with that enrolled in the qualitative study protocols.

Additional SEALD comments:

Our preliminary review of your submission concludes that you have included many of the necessary elements to support the content validity of the Psoriasis Diary as a measure of the important patient-reported psoriasis signs and symptoms in patients with moderate to severe plaque psoriasis. The Psoriasis Diary also includes items regarding the impacts of psoriasis (e.g., embarrassment), which do not appear to be targeted for labeling claims. Symptoms and impacts related to psoriatic nail changes and psoriatic arthritis are not covered by the instrument.

These comments do not represent our final comments, but our review findings to date. A final FDA review will follow our review of your final PRO instrument dossier that includes the psychometric testing.

We have the following comments on the development of the tool at this time.

- It will be useful to evaluate the signs and symptoms separately from the symptom impacts (i.e., using separate scores), because the patient-reported signs and symptoms are more closely linked to the hypothesized effects of the treatment. In addition, the submission states

(b) (4)

- The item “how noticeable did you think the color of the psoriasis-affected skin was in the last 24 hours” was taken to mean “noticeable by others” by some participants in cognitive interviews and can be affected by external factors (e.g., whether or not clothing is worn that day that covers the lesions). Items such as this will not be useful for product labeling.
- Plaque color can vary considerably across skin types and also during the day depending upon when the patient baths or showers and applies topical treatments and it is unclear whether patients can reliably report on this concept. For example, it is unclear whether instructions to patients will include (a) how to rate their skin (e.g., by looking in the mirror to also assess their backs) and (b) when to assess skin color (e.g., in relation to bathing / showering). It is possible that patients will weight the visible areas more heavily compared with the covered areas.
- The reduced mobility of hands in the target patient population was frequently reported in qualitative studies and may be attributed to psoriatic skin changes and/or underlying psoriatic arthritis. Please also address whether there are usability issues related to the electronic device.
- Please provide ATLAS.ti summaries sorted by symptom categories and other concepts. To facilitate review of patient-level data, please also provide summaries of quotations sorted by patient ID and include subject characteristics such as age, gender, race and concomitant diagnoses (e.g., psoriatic arthritis).

**Question 8:**

Is the phase III program outlined in psoriasis sufficient to claim the proposed indication?

“*Tradename is indicated for the treatment of moderate to severe (b) (4) plaque-type psoriasis in adult patients who are candidates for systemic therapy or phototherapy*”

**Response:**

The proposed claim appears reasonable based upon the information provided to date.

**Meeting Discussion:**

**In all clinical studies, the impact of administration of topical products, including emollients, OTC products, and concomitant prescription therapies should be described and evaluated. Inclusion and exclusion criteria should specifically address these issues.**

**Question 1:**

Is the phase III study CAIN457A2302 (see Appendix 6 for study synopsis) adequately designed to assess the efficacy and safety of secukinumab (AIN457) in the target population, with respect to the co-primary endpoints, secondary endpoints, sample size, dose regimens, statistical methodology, and inclusion/exclusion criteria?

**Response:**

You have submitted only Phase 3 protocol synopses in the briefing package. It is difficult to provide detailed comment. The following comments are meant to provide guidance on your future Phase 3 program.

Your proposed co-primary endpoints for the 12 week efficacy assessment, PASI 75 response and IGA of clear or almost clear, are acceptable.

You listed many secondary endpoints. It should be noted that secondary endpoints should be clinically meaningful, limited in number, and adjusted for multiplicity to control the Type I error rate.

It is unclear that the dosage selected for your Phase 3 trials is optimized. Your 300 mg dose has not been evaluated in Phase 2 trials for the treatment of psoriasis and the assumptions in your modeling may not directly reflect actual clinical use. Additional dose-ranging evaluations considering alternative doses, and/or different treatment duration(s), different frequency of use would assist in dose optimization.

Subjects with psoriasis  $\geq 10\%$  of BSA and IGA score  $\geq 3$  and a PASI  $\geq 12$  may be appropriate for systemic therapy and for enrollment for the indication of moderate to severe chronic plaque psoriasis.

Routine ECG monitoring in Phase 3 should be sufficient to detect a significant cardiovascular effects. This monoclonal antibody does not need to be evaluated in a thorough clinical QT study.

The protocol synopsis for Phase 3 trials, which proposes a graphical approach for multiplicity adjustment to control Type I error rate, appears to be acceptable, no details were given about randomization, analysis population, handling missing data as well as other aspects of the statistical analysis plan. The Agency will provide detailed comments when you submit your full protocol for future Phase 3 trials upon completion of Phase 2.

**Question 2:**

Is the phase III study CAIN457A2303 (see Appendix 7 for study synopsis) adequately designed to assess the efficacy and safety of secukinumab (AIN457) in the intended population, with respect to the co-primary endpoints, secondary endpoints, sample size, dose regimens, statistical methodology, and inclusion/exclusion criteria?

Is it acceptable that patients that have been on etanercept or placebo (in maintenance) and finish the 52-week treatment period are partially unblinded, since they are not eligible for entering the extension study?

**Response:**

See response to question 1, 3 and 4.

It appears that the partial un-blinding of the subjects described above will be acceptable for the extension study.

**Question 3:**

Assuming positive and clinically relevant differences between secukinumab and etanercept were achieved in study CAIN457A2303, (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

Trials utilizing comparator products should use the U.S. approved drug/biological product.

**Question 4:**

[Redacted] (b) (4)

**Response:**

See response to question 3.

**Question 5:**

Is the phase III study CAIN457A2304 (see Appendix 8 for study synopsis) adequately designed to assess the efficacy and safety of two different secukinumab (AIN457) regimens in the intended population, with respect to the primary endpoint, secondary endpoints, sample size, dose regimens, statistical methodology, and inclusion/exclusion criteria?

**Response:**

See response to question 1.

Your endpoint for relapse of treatment appears to be based on a loss of PASI. The Agency recommends that the same efficacy endpoints should be used for all comparisons throughout the trials. The study should be designed so that the results would identify which patient group, if any, would benefit from each regimen.

The Agency agrees with assessing relapse as a dosing parameter. Patient selection for each dosing regimen should be addressed.

You propose to conduct non-inferiority testing to compare the start of relapse regimen versus the maintenance regimen with fixed interval of AIN457 with respect to maintenance of response in subjects with moderate to severe chronic plaque psoriasis who are PASI75 responders at Week 12. The Agency considers such comparison to be exploratory.

**Meeting Discussion:**

**The sponsor should consider how relative changes in PASI scores are clinically meaningful. Statistical changes in PASI should have adequate clinical correlation. The sponsor stated IGA assessments would be considered.**

**Question 6:**

Study CAIN457A2304 will assess both (1) continuous fixed time-interval dosing, and (2) treatment on start of relapse dosing regimens. This is to assess if there will be additional benefit in the availability of two different treatment paradigms so as to allow for an individualized dosing regimen for patients and prescribers. Does the Agency agree with this approach?

(b) (4)

**Response:**

See response to question 5.

The Agency agrees with assessing relapse as a dosing parameter. Patient selection for each dosing regimen should be addressed (the study should be designed so that the results would identify which patient group, if any, would benefit from each regimen). The Agency recommends that the same efficacy endpoints should be used for all comparisons throughout the trials.

**Question 9:**

The psoriasis studies CAIN457A2302, CAIN457A2303, and CAIN457A2304 do not directly assess whether patients who do not respond to the 150 mg regimen would respond (if up-titrated) to the 300 mg regimen. However, differential response rates may be achieved by the 150 mg vs. the 300 mg regimen (see Section 3.6).

While not directly assessed, if the actual data does reflect that 300 mg gives a greater efficacy outcome with little additional risks from a safety perspective, could one of the outcomes from phase III program be a dose titration recommendation? For example, patients not responding to the 150 mg dose may be escalated to 300 mg.

**Response:**

It may be possible for a comparison of response rates to support titration of dose in conjunction with your proposed partial/ non-responder study. You are encouraged to complete a Phase 2

program which includes adequate dose ranging, addressing dose, duration, frequency and dosage form of administration. The Agency recommends response rates be assessed on both the IGA scale and PASI responses.

**Question 10:**

[REDACTED] (b) (4)  
?

**Response:**

[REDACTED] (b) (4)

**Question 11:**

Does the Agency agree that Novartis' plan to address FDA's comments regarding the assessment of the impact of secukinumab (AIN457) on the immune system, i.e. potential effect on T-cells and immune response, is adequate?

**Response:**

The T cell assessments from study CAIN457A2212 have not been provided to the Agency. These data, as well as the T cell assessment data from the psoriatic arthritis and ankylosing spondylitis studies will need to be reviewed by the Agency to determine if additional recommendations are forthcoming.

The utility of the CAIN457A2224 study which provides for assessment of immune response to vaccinations in healthy subjects in healthy volunteers is not clear. It may be likely that the immune response of psoriasis patients may not be the same as healthy volunteers, and patients with this degree of psoriasis may have been impacted by other immunomodulatory agents in past treatments.

The Agency is unaware of data that demonstrates that antibody response in post vaccination assays correlates with disease protection. It is not clear that meaningful data will result from the conduct of this proposed vaccine trial. At this time, it is likely that labeling related to vaccine use would reflect the general CDC/ACIP recommendations.

The adequacy of your proposal is currently under review. Additional comments may be forthcoming after submission of your FACS results and immunization protocol. We recommend you provide rationale for your assessment of the impact of AIN457 on the immune system in support of product safety.

**Question 16:**

Novartis would like to explore a 6 month filing strategy with the Agency. Given the positive safety and efficacy of the product to date, Novartis is considering a 6 month data submission

from phase III supported by phase II data for 12 months. Assuming convincing safety and efficacy from a 6 month phase III analysis, would this be acceptable to the Agency?

**Response:**

No, your product will need to be fully characterized from a safety standpoint. A concern related to immunomodulation, is the potential for the development of long-term side effects such as malignancy. Therefore, the use of AIN457 represents a situation in which there is a need for a longer-term safety data base in order to detect late developing adverse drug events or adverse drug events that increase in severity or frequency over time.

Furthermore, it is not clear that the experience in other indications can be extrapolated to adequately support safety the moderate to severe plaque psoriasis population.

**Question 17:**

Novartis is planning an additional phase III study CAIN457A2307. The objective of this study will be to assess if partial or non responders to the phase III proposed subcutaneous regimen could be converted to responder status by high intravenous doses. This approach is based on the results of study CAIN457A2212. Is study CAIN457A2307 adequately designed to assess the efficacy and safety of intravenous secukinumab in the target population, with respect to the primary endpoint, secondary endpoints, sample size, dose regimens, statistical methodology, and inclusion/exclusion criteria?

Would this study, supported by the remainder of the phase III program outlined above, and considering that the formulation for the intravenous administration will be the same lyophilisate used in the subcutaneous program, be sufficient to support this additional route of administration for registration in this partial and non-responder population for registration?

**Response:**

You have provided little detail regarding this protocol (no protocol or synopsis is provided) thus limiting our response. We recommend that with the protocol submission, you provide your rationale to support your position that data from subcutaneous administration supports intravenous administration.

**Question 18:**

Is the Novartis justification for a deferral in pediatrics development for psoriasis (see below) sufficient and appropriate? Furthermore, do the proposed studies in children and adolescents 6-17 years of age meet FDA's requirement for the clinical evaluation of secukinumab (AIN457) in children and adolescents?

**Response:**

Your approach to obtain adequate adult safety and efficacy data prior to proceeding with trials in pediatric psoriasis subjects is reasonable given the anticipated safety profile of secukinumab. The pediatric risk benefit assessment at that time (projected to be 2014) will depend on not only your experience with adult psoriasis subjects, but will also be informed by the experience in

pediatric subjects in other indications sought for your product. It is premature to provide specific comments on the two pediatric trial synopses.

Additionally, see response to question 15.

Additional Pharm/Tox Comments (including comments previously sent to the sponsor on March 17, 2010):

1. Your most recent annual report, received by the Agency on February 10, 2011, references several completed nonclinical studies for which final study reports have not been submitted to the Agency. Please submit these final study reports as soon as they are available.
2. The Agency has determined that the NOAEL in the 26 week monkey study is 50 mg/kg/week (not 150 mg/kg/week) due to the immunotoxicity observed in this study.
3. We note that the draft study reports submitted for studies 502618 and 502774 did not include TDAR or IL-17 analysis data. Please submit to the IND the final study reports, including the TDAR and IL-17 analysis data, as soon as they become available.
4. While the Agency agrees that no additional nonclinical studies are needed to address the carcinogenic potential of AIN457, the immunosuppressive properties of AIN457 will need to be adequately addressed in the label. Pharmacovigilance alone may not be adequate to address the issue of carcinogenicity. A registry study may be needed to assess malignancies after chronic use in humans. This will remain a review issue likely to be addressed upon BLA submission.
5. We acknowledge that you have submitted a literature summary to the IND. However, you should provide the literature references addressing effects of IL-17a inhibition and potential carcinogenic risk. This information will be needed for labeling purposes. The published literature could provide information from transgenic, knock-out, animal disease models or human genetic diseases to assist with understanding the potential carcinogenic risk associated with AIN457.

#### **Additional Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. You are encouraged to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for Phase 3 trials. Comments on phase 1 and 2 trials do not necessarily constitute commitments that can be extrapolated to Phase 3 trials.
3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
6. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

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

/s/  
-----

SUSAN J WALKER  
03/15/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 100,418

**MEETING MINUTES**

Novartis Pharmaceuticals Corporation  
Attention: Shilpa Kurpad, Pharm.D.  
Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Kurpad:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AIN 457, for the treatment of moderate to severe plaque type psoriasis.

We also refer to the teleconference between representatives of your firm and the FDA on July 15, 2009. The purpose of the meeting was to discuss the development of your PRO tool.

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

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

*{See appended electronic signature page}*

Stanka Kukich, M.D.  
Deputy Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Official Meeting Minutes

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** July 15, 2009  
**TIME:** 9:00 a.m. EDT  
**LOCATION:** Teleconference  
**APPLICATION:** IND 100,418  
**DRUG NAME:** AIN 457  
**TYPE OF MEETING:** Type C General Guidance

**MEETING CHAIR:** Stanka Kukich, M.D.

**MEETING RECORDER:** Paul Phillips

**FDA ATTENDEES:** (Title and Office/Division)

Stanka Kukich, M.D., Deputy Director, DDDP  
David Kettl, M.D., Clinical Team Leader, DDDP  
Amy Weitach, D.O., Clinical Reviewer, DDDP  
Elektra Papadopoulou, M.D., Medical Officer, SEALD  
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

**EXTERNAL CONSTITUENT ATTENDEES:**

Christian Antoni, Global Program Head  
Charis Papavassilis, Global Program Medical Director  
Judit Nyirady, Medical Director, Dermatology, US  
Andrine Swensen, Director, Evidence-Based Medicine  
Jie Zheng, Associate Director, Evidence-Based Medicine  
John Cutt, Vice President, Drug Regulatory Affairs, Immunology and Infectious Diseases  
David AD Jones, Global Program Regulatory Director  
Mercy Mathew, Post Doctoral Fellow, Drug Regulatory Affairs  
Shilpa Kurpad, US Regional Brand Regulatory Manager

**BACKGROUND:**

This meeting was requested to discuss the development of the sponsor's PRO tool.

**DISCUSSION POINTS:**

**Clinical/ SEALD**

**Question 1:**

Does the FDA concur that Novartis is following an appropriate development process for a psoriasis signs and symptoms daily diary that will be fit for the purpose of evaluating the signs and symptoms and the impact of psoriasis treatment on patient health and functioning?

**Response:**

We cannot concur, because critical elements for full assessment did not appear in the submission. These are exemplified by the comments below.

- Without a copy of the PRO instrument, the Agency cannot comment on the tool’s content validity. Content validity is defined in the draft PRO guidance for industry as evidence from qualitative research demonstrating that a PRO instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. As stated below, content validity is important to establish prior to assessment of the tool’s other measurement properties.
- It is unclear whether you are targeting only “signs and symptoms” or “signs, symptoms and impacts” of psoriasis for labeling claims. In the table of your briefing book entitled, Linking Label Goals to Measurement Concepts and Measures, it appears that only the signs and symptoms (Pain, Itching, Flaking, Stinging, Tearing and Cracking, Skin Color) (b) (4). It is acceptable to target only the signs and symptoms, without the disease impacts. However, the focus should be on signs and symptoms that cannot be measured by a physician (e.g.: itching and pain). The measurement goals should be clarified, because the submission appeared to be internally inconsistent in describing whether or not the impacts were also being targeted.
- The concept elicitation report provided was a preliminary report and did not contain the appendices. Therefore, certain elements from the qualitative research done could not be reviewed. For example, although it appears that saturation was reached in the concept elicitation interviews, a saturation table with all symptoms and impacts listed was not appended. Other documents describing early instrument development (e.g., interview guides) were also not available for in-depth Agency review in the current submission.
- There was not a description of disease characteristics (including BSA involvement) and location of lesions in the preliminary study report. It is also helpful to have documentation of the disease history and to know whether or not patients consider their disease as currently stable. Such information should be included to allow assessment of whether the range of disease characteristics in the interviewed subjects is reflective of the range expected in the target study population. In addition, evidence of saturation is incomplete without a report of the disease severity and characteristics of the sample of patients interviewed.
- The preliminary concept elicitation report suggested that some patient interview data may have been excluded from consideration, because the data were based on patients that “do not entirely characterize the intended patient population of this program.” If patient interview data were excluded, the excluded data should be described and the rationale provided.
- Preferably, the completion of the diary should take place at the same time each day and at the same time in relation to bathing or showering. This information was not described.

**Question 2:**

Does the FDA agree that the specified PRO concepts have been adequately evaluated for their relevance and importance from the perspective of experts, existing research, and patients with chronic plaque psoriasis?

**Response:**

No. We cannot agree without complete information including summary of transcripts of patient interviews and discussions with experts. We also have concerns as described in item 3 below.

**Question 3:**

Does the FDA agree that the specified PRO concepts could be in the future (dependent on results) reflected in the product labeling?

**Response:**

You have [REDACTED] (b) (4). We recommend targeting only those claims which are based on well-defined and reliable endpoints. Appropriateness will depend upon the results of the qualitative research and other sources including expert input.

However, it is still unclear how these measurement concepts were developed. It is unclear what is being measured by the term “skin color,” for example. “Skin color” may reflect color changes (e.g., erythema) due to active psoriatic lesions, but also may reflect postinflammatory pigmentation, which can be persistent for long periods of time and might manifest differently depending on the skin type. It may not be feasible to have patients rate the color of their psoriatic lesions, unless it can be shown that patients can reliably and validly do so.

[REDACTED] (b) (4)

**Question 4:**

Does the FDA agree with the key parameters for ‘how’ to best measure the identified PRO concepts; that is, the parameters of the PRO measurement strategy?

**Response:**

You have proposed measurement of the following: (a) frequency, (b) duration and (c) severity. In general, these parameters appear appropriate depending on the disease symptom or disease impact being assessed and the frequency of assessments.

**Question 5:**

Does the FDA agree that Novartis should return to discuss the PRO instrument once it has been developed and its measurement properties have been evaluated in the AIN457 Phase 2b trial?

**Response:**

We suggest you seek FDA advice once the draft instrument is developed and all qualitative research is documented and summarized. This should occur prior to instrument finalization and further psychometric testing (e.g., in the phase 2b study). Without a copy of the draft PRO instrument and full documentation of the qualitative research to establish content validity, the Agency cannot comment on the tool’s content validity. It is important to establish content validity prior to assessment of the tool’s other measurement properties in the phase 2b study, because testing the tool’s other measurement properties will not replace or rectify problems with content validity.

### **Additional Clinical Comments**

1. We recommend establishing baseline symptom severity by inclusion of a run-in period in the clinical trial study design.
2. We recommend clarification of planned data capture methods (e.g., paper and pencil diary, electronic data capture, IVRS). As a matter of policy we do not require one over another at this time. However, it is useful to clarify which method is planned.

### **Meeting Discussion:**

The Agency has not received the draft PRO instrument for our review and comment. Without this document we could not make any agreements concerning the adequacy or validity of the instrument. The qualitative and content validation is critical. Without this an instrument can not support labeling claims. Qualitative research needs to be done in populations reflective of the target patient population with psoriasis. The sponsor should submit the draft PRO instrument for review and comment.

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 100418

-----  
NOVARTIS  
PHARMACEUTICALS  
CORP

-----  
AIN457

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

/s/  
-----

STANKA KUKICH  
07/22/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 100,418

Novartis Pharmaceuticals Corp.  
Attention: Shilpa Kurpad, Pharm.D.  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Dr. Kurpad,

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AIN 457, indicated for treatment of psoriasis.

We also refer to the teleconference between representatives of your firm and the FDA on May 27, 2009. The purpose of the meeting was to discuss the planned Phase 2b protocol for study AIN457A211.

A copy of the official minutes of the teleconference is attached 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) 796-3935.

Sincerely,

*{See appended electronic signature page}*

Susan J. Walker, M.D., F.A.A.D.  
Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** May 27, 2009  
**TIME:** 9:00 a.m.  
**LOCATION:** Teleconference  
**APPLICATION:** IND 100,418  
**DRUG NAME:** AIN 457  
**TYPE OF MEETING:** Type C Guidance

**MEETING CHAIR:** Susan Walker, M.D.

**MEETING RECORDER:** Paul Phillips

**FDA ATTENDEES:** (Title and Office/Division)

Susan Walker, M.D., Director, DDDP  
David Kettl, M.D., Clinical Team Leader, DDDP  
Amy Woitach, D.O., Clinical Reviewer, DDDP  
Carmen Booker, Ph.D., Pharmacology Reviewer, DDDP  
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DB III  
Carin Kim, Ph.D., Biostatistics Reviewer, DB III  
Dennis Bashaw, Pharm.D., Director, DCP III  
Seongeun Cho, Ph.D., Clinical Pharmacology Reviewer, DCP III  
Barbara Rellahan, M.S., Ph.D., Product Quality Team Leader, DMA  
Rashmi Rawat, Ph.D., Product Quality Reviewer, DMA  
J. Paul Phillips, M.S., Regulatory Project Manager, DDDP

**EXTERNAL CONSTITUENT ATTENDEES:**

Charis Papavassilis – Global Program Medical Director  
Christian Antoni – Global Program Head  
Judit Nyirady – Medical Director, Dermatology, US  
Nathalie Barbier – Senior Expert Statistician  
Andrew Wright - Expert Statistician  
Frank Brennan - Principal Safety Assessment Expert  
Gerardus J.M. Bruin - Drug Metabolism and Pharmacokineticist  
Hanno Richards – Senior Translational Medicine Expert  
Michaela Dehio - Technical Project Leader  
John Cutt - US Regulatory Head, Immunology and Infectious Diseases  
David A.D. Jones - Global Program Regulatory Director  
Shilpa Kurpad - US Regional Brand Regulatory Manager

## **MEETING OBJECTIVES:**

Discuss the planned Phase 2b protocol for Study AIN457A2211 included in the April 24, 2009 briefing package.

## **DISCUSSION POINTS:**

### **General Comments**

The responses to your submitted questions are general comments for guidance in your product's phase 2 development, and do not constitute commitments that can be extrapolated to phase 3 trials. You are encouraged to request and attend an End-of-Phase 2 meeting to obtain regulatory agreements for clinical endpoints and study design for phase 3 trials at the appropriate juncture once your phase 2 safety and efficacy data has been reviewed.

The Division requests that the following issues be addressed in the clinical development of your product for the treatment of plaque psoriasis, acknowledging the relapsing, remitting nature of the natural history of the disease, and the likelihood that your product may have chronic, intermittent use over extended periods of time:

1. You are required to provide adequate nonclinical data to support dosing in clinical investigations for both the initiation and maintenance phases of your product's proposed treatment. See specific Pharmacology/Toxicology comments below.
2. Dose ranging should be conducted in a manner which investigates the induction/loading phase separately from the maintenance phase, as dosing for maintenance or re-treatment upon relapse may be different than that required for the initial treatment phase. In early development, you are encouraged to fully explore dose ranging in order to select a dose that maximizes safety and efficacy for the different treatment periods you propose. Dose ranging studies should investigate safety and efficacy and incorporate all elements of dose ranging such as dose (concentration), frequency, and duration of therapy. Adequate dose ranging explorations in phase 2 would allow determination of the formulation most likely to succeed in phase 3 with optimal risk/benefit profile (safety outcomes). Informational needs would include the assessment of differences between maintenance of effect, and re-treatment upon relapse, as well as disease response for treatment free intervals as the natural course of psoriasis includes the potential for waxing and waning of symptoms.

Product toxicity is likely related to cumulative product exposure over time, and you should conduct longer term trials to determine how your product will be used for maintenance therapy or re-treatment upon relapse. In order to ensure the public health investigations should address duration of effect and various dose concentrations and frequencies to be used for treatment of this chronic disease. Clinical trial data should be provided to elucidate the effects of long-term immunosuppression on both safety and

efficacy. You should provide information concerning the duration of clinical trial data that you believe should be provided prior to approval of your biologic product.

**Meeting Discussion:**

The sponsor noted that their proposed dose was governed by the physical ability to administer a 1 mL subcutaneous dose, and not related to any clinical assessment. They plan to assess different exposures by changing the frequency of dosing rather than alternative dose regimens. The sponsor indicated that they had no additional plans for dose-ranging or weight based dosing. The Agency indicated that the dose ranging as proposed may not be adequate to support Agency agreement on study design for Phase 3 trials.

3. You should propose a mechanism to assess the immunosuppressive effect of your product over time by demonstrating the extent of immunosuppression, its duration, and determining the recovery rate and characteristics of immunologic function as it returns to baseline.

**Meeting Discussion:**

The Agency asked the sponsor to provide a plan of assessments for how they intend to document the immunosuppressive effects during treatment and recovery of immune function after withdrawal from the drug.

**CMC**

There are no specific product questions in the briefing document and there are no comments regarding the proposed phase 2 protocol at this time.

**Pharmacology/Toxicology**

1. You should submit the 13 week subcutaneous and 26 week intravenous monkey study reports for review prior to initiation of the proposed Phase 2b clinical study with a treatment duration of 36 weeks. The proposed Phase 2b clinical study would be placed on clinical hold if these nonclinical toxicology study reports are not submitted to the IND with adequate time for review prior to initiation of the proposed Phase 2b clinical study.
2. You should submit the subcutaneous monkey embryofetal development study for review prior to initiation of Phase 3 clinical studies.
3. Your proposal for conduct of the mouse fertility study and the mouse peri- and post-natal development study with the surrogate murine antibody targeting IL-17A may be acceptable provided adequate data is submitted to assure that the surrogate murine antibody binding to mouse IL-17A is similar to AIN457 binding to human IL-17A. The mouse fertility study should be conducted prior to initiation of Phase 3 clinical studies and the mouse peri- and post-natal development study should be conducted prior to the BLA submission.

4. Treatment of psoriasis is a chronic indication and the carcinogenic potential of AIN457 should be assessed to support the marketing of your biologic product. You should submit your proposal for evaluation of the carcinogenic potential associated with AIN457 prior to initiation of long-term clinical studies. Final study reports that address the carcinogenic potential associated with AIN457 should be included with the BLA submission for the psoriasis indication. One possibility could be conduct of a mouse carcinogenicity study with the available surrogate murine antibody targeting IL-17A.

**Meeting Discussion:**

The sponsor indicated there was a recent submission of final study reports to the Agency. The Agency agreed to review those reports and send comments upon completion of the review.

**Clinical Pharmacology/Biopharmaceutics**

The sponsor states that the objective of the planned phase 2b study, CAIN457A2211, is to find a dose and a dose-regimen for AIN457 in the treatment of psoriasis. However, the Agency is concerned that the submitted protocol is based on a number of pharmacokinetic assumptions, and a simulation from limited human data.

- The steady-state dose-exposure simulation is drawn from IV and SC data from monkey (both given at 150 mg/kg). The subcutaneous layer and the skin structure in monkey are different from human and it will be important to know how the drug will behave IV vs. SC in man. In addition, the cross-reactivity of the drug antibody with cyno monkey's IL-17A is 100-fold lower than that with human's and this difference may affect the rate of systemic and tissue clearance of the antibody, which should be considered in PK simulation.
- Dose-proportionality and the elimination linearity of AIN457 are currently unknown. Since biologics often demonstrates non-linear PK, the sponsor should consider dose-ranging evaluation in phase 2 and establish a dose-exposure relationship prior to an initiation of phase 3 trials. The on-going CAIN457A2204 and CAIN457A2212 studies with an IV formulation did not include PK arms, which would have provided useful data to this end.
- Immunogenicity and an induction of anti-product antibody should be considered as they may affect drug clearance. It can not be adequately predicted from non-preclinical species or following a single application.
- Based on the reasons above, it is premature for the Agency to comment on the protocol, and the Agency recommends the dose selection and dose regimen are determined after the completion of CAIN457A2203. Depending on the result of the study, you may be required for additional information. The sponsor is reminded that a properly designed phase 2b study is critical in selecting optimal doses for phase 3 trials.

*Regarding CAIN457A2203 (ongoing bioavailability study comparing SC to IV):*

The sponsor is conducting a randomized cross-over BA study with 1 mg/kg IV, followed by 150 mg SC. The wash-out period however is only 29 days, which is around the half life of the drug. Therefore carry-over effects are to be expected.

- The sponsor should provide a secondary analysis of the first period treatment data (7 IV subjects vs. 7 SC subjects) in a cross-treatment manner. This would inform the degree of carry-over effects present in the cross-over portion of the data, albeit limited due to the small nature of the parallel treatments in the first phase.
- The sponsor should also provide a detailed explanation of how they will control and/or "adjust" their data in their PK analysis for the potential accumulation of the drug during the second phase.

**Meeting Discussion:**

The sponsor indicated that the BA trial had recently been completed and PK data obtained. The Agency stated that the data would need to be submitted for formal review before any comment could be made. The sponsor agreed to submit the data.

**Clinical/Biostatistics**

**Question 1:**

Does the Health Authority agree that the overall design of this study will be adequate for dose & regimen finding before Phase 3 regarding dose and dose regimen (initial and maintenance)?

**Response:**

Selection of the appropriate dose should be based on the safety and efficacy profile of the drug which might be based on pre-clinical as well as clinical data. Further, selection of the appropriate dose should take into account the drug concentration, frequency of use, and treatment duration. The sponsor's current approach for dose selection is aimed for treatment as well as maintenance periods. However, the proposed design might not be an efficient design as the proposed design implies that only the subjects in the selected dose group will be utilized and investigated for the maintenance period. The sponsor should first consider selecting an appropriate dose for the treatment period based on efficacy/safety data for the treatment period. Then upon selecting an appropriate dose for the treatment period, the sponsor should conduct an adequate dose-ranging study for the maintenance period separately. In this regard, the sponsor should consider the following points in selecting an appropriate dose for the maintenance period.

- 1) Criteria for relapse need to be prespecified along with visit-plan to assess subjects to verify whether they meet the relapse criteria to be eligible for treatment.
- 2) An appropriate dose for the maintenance period might have different concentration and frequency of use than that of the treatment period.

It is also important in phase 2 to study PK parameters, refine endpoints, and explore treatment effects for powering phase 3 studies. Phase 2 studies will further assess the performance of your product and allow testing of hypotheses in phase 3 based on both the safety and efficacy

assessments. Phase 2 dosing schedules should be based primarily on safety considerations until the adverse event profile of your product is more fully characterized.

From the limited clinical experience with your product for psoriasis provided to date, this single trial will not provide adequate information regarding various aspects of dose, duration and frequency of dosing for this new molecular entity. The rationale for the proposed dose of 150 mg throughout all arms of the proposed phase 2 study should be supported by an assessment of safety from additional trials, and it may prove useful to also examine weight based dosing vs. fixed single dosing based on safety experience in other trials.

Additionally, the risk benefit profile for plaque psoriasis may prove to be different from other indications that are sought for this product. Adequate explorations of product safety will be required for chronic, intermittent dosing, and this would include nonclinical support as well as review of clinical experience for all available indications.

**Question 2:**

Does the FDA agree with the justification and use of the sponsor proposed revised IGA 6-point rating scale?

**Response:**

The sponsor plans to use PASI 75 response rate as the primary efficacy endpoint in the planned Phase 2 trial and success in IGA on a 6-point scale as the primary efficacy endpoint in their future Phase 3 trials. While the 6-point scale might be acceptable for Phase 2 trial, it should be noted that a reliable estimate of treatment effect derived from Phase 2 trials using success on IGA would be required to power Phase 3 trials. To get reliable estimates, the Phase 2 trial should have the same enrollment criteria and IGA scale as those planned for the Phase 3 trials.

As previously communicated, the Agency continues to recommend a 5-point static IGA scale. The preference for a 5-point scale is based on the success criteria of achieving “clear” or “almost clear” combined with 2 points reduction on the scale. Assuming the scale is linear (i.e., equal length categories), a 2-point reduction on a 5-point scale is more clinically meaningful than that on a 6-point scale. Also, for enrollment criteria, a specific minimum score implies a slightly higher severity on the 5-point scale compared with that on the 6-point scale.

**Question 3:**

Does the FDA agree with the other endpoints of this study?

**Response:**

For the proposed study, the sponsor listed several secondary endpoints. While this is acceptable for Phase 2 trials, it should be noted for Phase 3 trials, the number of secondary endpoint should be limited to those that are clinically meaningful, and multiplicity adjustment should be planned to control the Type I error rate.

Agreements on phase 3 trial endpoints will be made at the End of Phase 2 meeting at the appropriate juncture in your product’s development.

**Question 4:**

Does the Health Authority agree with the assessment of treatment upon relapse as an appropriate secondary endpoint? Does the agency have any opinion regarding the utility of this type of treatment in this indication i.e. flexibility beyond routine scheduled maintenance posology for prescribers and patients?

**Response:**

Sponsors are free to explore various endpoints in phase 2 studies. It seems reasonable that future flexible treatment regimens would first require demonstration of safety and efficacy for the primary induction/loading endpoint. Dose ranging and adequate safety information for any “flexible” therapy would be necessary to properly assess the risk benefit analysis for chronic treatment of plaque psoriasis.

Explorations of variable drug withdrawal and retreatment timeframes will be important to assess the safety of your product, but will present complex statistical issues to validate efficacy. These would need to be fully explored in phase 2 prior to agreement on the design of phase 3 protocols.

**Question 5:**

Does the Health Authority agree with the statistical methodology and sample size?

**Response:**

- The study planned several analyses for the primary endpoint and the study was powered taking into account the four treatment arms using the Bonferroni correction method. For Phase 2 trials, no formal statistical testing is required and consequently, the study does not need to be powered. However, the study should not be small so that reliable estimates of treatment effect can be obtained to be used for planning future Phase 3 trials.
- The study planned to conduct several comparisons for data (A1 vs. A2, B1 vs. B2, C1 vs. C2, A1+C1 vs. A2+C2) following the primary time point at week 12. While the sponsor could investigate different comparisons for Phase 2 trials, the Agency views such comparisons as exploratory.
- The sponsor proposed to use the last observation carried forward (LOCF) approach. While the propose approach is acceptable for Phase 2 trials, it should be noted that for Phase 3 trials, the sponsor should propose sensitivity analyses so as to ensure that the results are not driven by the imputation method used.

**Question 6:**

Does the Health Authority agree with our proposal to perform an interim analysis?

**Response:**

The sponsor stated that they plan to do an interim analysis when the 100 patients randomized to maintenance arms reach week 28 to decide on dose regimen for Phase 3 trials. While results from Phase 2 trials are useful, for planning future Phase 3 trials, the sponsor might conduct an

interim analysis if they desire on their planned Phase 2 trial. It should be noted, however, that establishing efficacy for the drug will be based mainly on the findings of future Phase 3 trials.

### **Additional Clinical Comments**

Provide all available clinical safety data for all indications studied to date to the IND.

Until the safety profile of this new molecular entity is further characterized, the Agency continues to recommend exclusion of subjects who do not have normal hematological and metabolic lab values, including creatinine levels. Subjects with chronic plaque psoriasis tend to be a younger, healthy population and entry criteria should reflect that population.

Until the adverse event profile of your product is more fully characterized, the Agency continues to recommend a 15% body surface area of psoriasis for inclusion into your product's trials.

### **Meeting Discussion:**

The sponsor agreed to provide the additional clinical safety data for all indications studied to date.

### **Additional Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
5. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety

and effectiveness data “by gender, age, and racial subgroups” in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.

6. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.
7. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).
8. You are encouraged to request an End-of-Phase 2 Meeting at the appropriate time.

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 100418

-----  
NOVARTIS  
PHARMACEUTICALS  
CORP

-----  
AIN457

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

/s/  
-----

SUSAN J WALKER

06/04/2009

**LATE-CYCLE COMMUNICATION**  
**DOCUMENTS**



BLA 125504

**LATE-CYCLE MEETING MINUTES**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Director, Drug Regulatory Affairs  
One Health Plaza  
Building 135, Office 414  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

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

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on October 8, 2014.

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

If you have any questions, call Matthew White, Regulatory Project Manager at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD  
Clinical Team Leader  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure:  
Late Cycle Meeting Minutes



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

---

**MEMORANDUM OF LATE-CYCLE MEETING MINUTES**

**Meeting Date and Time:** October 8, 2014 at 10:00 a.m.  
**Meeting Format:** Teleconference

**Application Number:** BLA 125504  
**Product Name:** COSENTYX™ (secukinumab)  
**Applicant Name:** Novartis Pharmaceuticals Corporation

**Meeting Chair:** David Kettl, MD  
**Meeting Recorder:** Matthew White

**FDA ATTENDEES**

Julie Beitz, MD, Director, ODE III  
Tatiana Oussova, MD, MPH, Acting Director, DDDP  
Kendall A. Marcus, MD, Acting Deputy Director for Safety, DDDP  
David Kettl, MD, Clinical Team Leader, DDDP  
Amy Woitach, DO, MS, Clinical Reviewer, DDDP  
Jill Merrill, PhD, Pharmacology Reviewer, DDDP  
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III  
Carin Kim, PhD, Biostatistics Reviewer, DB III  
Yow-Ming Wang, PhD, Clinical Pharmacology Team Leader, DCP3  
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3  
Sarah Kennett, PhD, Review Chief, DMA  
Tura Camilli, PhD, Product Quality Reviewer, DMA  
Reyes Candau-Chacon, PhD, Product Quality Microbiology Reviewer, BMAB  
Felicia Duffy, RN, BSN, MSED, Risk Management Analyst, DRISK  
Carolyn McCloskey, MD, Medical Officer, DEPI I  
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III  
Matthew E. White, Senior Regulatory Health Project Manager, DDDP

**EASTERN RESEARCH GROUP ATTENDEES**

Chelsea (So Hyun) Kim, Independent Assessor

**APPLICANT ATTENDEES**

Jose Maria Gimenez Arnau, Sr. Global Program Head  
Charis Papavassilis, Sr. Global Program Medical Director  
Gerard Bruin, DMPK  
Nancy Landzert, Global Reg CMC  
Andreas Balzer, Technical Product Lead  
David A. D. Jones, Sr. Global Program Regulatory Director  
Katie Picone, Sr. Global Program Regulatory Manager

Becky Mancini, Sr. Global Program Regulatory Manager  
John Hohneker, Franchise Development Head  
George Vratsanos, Executive Global Program Head  
Ellen McCroskery, Franchise Drug Safety lead  
Mark Levick, Franchise Clinical Unit Head  
Penny Giles, Franchise Regulatory Head  
Rob Kowalski, Global Regulatory Head and US Development Head  
Diane Zezza, Global Regulatory CMC Head

## **1.0 BACKGROUND**

BLA 125504 was submitted on October 24, 2013 for COSENTYX™ (secukinumab).

Proposed indication(s): Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

PDUFA goal date: January 23, 2015

FDA issued a Background Package in preparation for this meeting on September 29, 2014.

## **2.0 DISCUSSION**

### 1. Introductory Comments

### 2. Discussion of Substantive Review Issues

- Dose/dosing regimen selection: The Agency is still considering the optimal dose/dosing regimen in order to achieve an optimal risk/benefit determination for secukinumab. This issue will be recommended for discussion by the Advisory Committee members.

Specifically, is the benefit of additional treatment effect observed in the 300 mg dosage arms sufficient to outweigh the potential short term and long term safety risks from the resulting increase in systemic exposure of secukinumab? And if so, should dosing recommendations be based on different patients' weight?

### 3. Discussion of Minor Review Issues

- Labeling discussions pending

### 4. Discussion of Upcoming Advisory Committee Meeting

### 5. REMS or Other Risk Management Actions

- No safety concerns have been identified that require a REMS to ensure safe use.

6. Postmarketing Requirements/Postmarketing Commitments

- a. **PREA PMR** – Conduct studies to evaluate the safety and efficacy of secukinumab in pediatric subjects with plaque psoriasis.
- b. **Clinical PMR** – Assess the risk of secukinumab-related delayed adverse events following long-term exposure.
- c. **Clinical Pharmacology PMC** – Conduct a clinical trial to assess whether secukinumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with secukinumab.
- d. **Product Quality PMC** – To re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
- e. **Product Quality PMC** – To re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
- f. **Product Quality PMC** – To re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
- g. **Product Quality Microbiology PMC** – To conduct routine bioburden testing (b) (4). 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.
- h. **Product Quality Microbiology PMC** – To conduct routine bioburden testing (b) (4). 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.
- i. **Product Quality Microbiology PMC** – To conduct routine bioburden and endotoxin testing (b) (4). Routine testing will be implemented for the 2015 manufacturing campaign.
- j. **Product Quality Microbiology PMC** – 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.
- k. **Product Quality Microbiology PMC** – To evaluate feasibility of (b) (4) secukinumab drug substance and update drug substance specification (b) (4).

## 7. Review Plans

- The Office of Compliance has given an overall recommendation of acceptable for the manufacturing sites.
- The Office of Scientific Investigation (OSI) inspection results are complete and appear adequate in support of the respective indication.
- We plan to take an official action in accordance with the PDUFA goal dates.

## 8. Wrap-up and Action Items

### **Meeting Discussion:**

The Agency requested that a fully updated module 3 be submitted to the BLA

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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

/s/  
-----

DAVID L KETTL  
10/14/2014



BLA 125504

**LATE CYCLE MEETING  
BACKGROUND PACKAGE**

Novartis Pharmaceuticals Corporation  
Attention: Katie Picone, PharmD  
Director, Drug Regulatory Affairs  
One Health Plaza  
Building 135, Office 414  
East Hanover, NJ 07936-1080

Dear Dr. Picone:

Please refer to your Biologics License Application (BLA) submitted under the Public Health Service Act for COSENTYX™ (secukinumab).

We also refer to the Late-Cycle Meeting (LCM) scheduled for October 8, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

*{See appended electronic signature page}*

Tatiana Oussova, MD, MPH  
Acting Division Director  
Division of Dermatology and Dental Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

ENCLOSURE:

Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** October 8, 2014 at 10:00 a.m.  
**Meeting Location:** Teleconference

**Application Number:** BLA 125504  
**Product Name:** COSENTYX™ (secukinumab)

**Proposed Indication:** Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy  
**Applicant Name:** Novartis Pharmaceuticals Corporation

### INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

### BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

#### Discipline Review Letters

No Discipline Review letters have been issued to date.

#### Substantive Review Issues

The following substantive review issues have been identified to date:

##### **Clinical/Clinical Pharmacology:**

Dose/dosing regimen

## ADVISORY COMMITTEE MEETING

**Date of AC meeting:** October 20, 2014

**Date AC briefing package sent under separate cover by the Division of Advisory Committee and Consultant Management:** September 29, 2014

**Potential questions and discussion topics for AC Meeting are as follows:**

- 1. Considering potential risks and benefits, do the available data support approval of secukinumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy?**

**Background Information for Consideration (Issue 1):** As the question states, we are asking the Committee to weigh all the risks and benefits in the vote for approval. Please note that a vote for approval, in general terms, does not mean that one must agree with all of the proposed dosing recommendations or that one must define all labeling recommendations. Questions 2 and 3 that follow the general approval question/vote will give the Committee a chance to provide opinions on more granular issues. If not, please consider what additional studies should be recommended.

- 2. Please comment on the strength of evidence for use of secukinumab at a dose strength of 300 mg for all patients independent of weight.**

**Background Information for Consideration (Issue 2):** The Phase 3 efficacy results showed that both 150 mg and 300 mg doses of secukinumab achieved significantly higher response rates compared to the placebo and the 300 mg dose achieved a higher response rate compared to the 150 mg dose. At the same dose, secukinumab serum concentrations were higher in subjects with a body weight < 90kg than those in subjects with a body weight ≥ 90 kg, and the clinical response rates were approximately 10% higher in the lower body weight group at both 150 mg and 300 mg doses. A limited number of observed adverse events, mostly infections, demonstrated an increasing trend with higher exposure. Should the recommended dose strength of secukinumab be 150 mg in the patient subgroup with body weight <90 kg? Should there be an exploration of the higher dose strength of 450 mg in the patient subgroup with a weight ≥90 kg?

- 3. Please comment on postmarketing studies/trials that are needed to further define the safety and/or efficacy of secukinumab, including, but not limited to the need for long-term studies to evaluate malignancy risk and whether alternative dosing strategies should be evaluated.**

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

## REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date. A REMS is not contemplated for this application.

## LCM AGENDA

1. Introductory Comments – 5 minutes
  - Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues – 5 minutes

Each issue will be introduced by FDA and followed by a discussion.

- Dose/dosing regimen selection: The Agency is still considering the optimal dose/dosing regimen in order to achieve an optimal risk/benefit determination for secukinumab. This issue will be recommended for discussion by the Advisory Committee members.

Specifically, is the benefit of additional treatment effect observed in the 300 mg dosage arms sufficient to outweigh the potential short term and long term safety risks from the resulting increase in systemic exposure of secukinumab? And if so, should dosing recommendations be based on different patients' weight?

3. Discussion of Minor Review Issues – 2 minutes

Labeling discussions pending

4. Discussion of Upcoming Advisory Committee Meeting – 10 minutes
5. Postmarketing Requirements (PMR)/Postmarketing Commitments (PMC) – 10 minutes
  - a. PREA PMR – Conduct studies to evaluate the safety and efficacy of secukinumab in pediatric subjects with plaque psoriasis.
  - b. Clinical PMR – Assess the risk of secukinumab-related delayed adverse events following long-term exposure.
  - c. Clinical Pharmacology PMC – Conduct a clinical trial to assess whether secukinumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with secukinumab.
  - d. Product Quality PMC – To re-evaluate secukinumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

- e. Product Quality PMC – To re-evaluate secukinumab drug product (vial) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
- f. Product Quality PMC – To re-evaluate secukinumab drug product (prefilled syringe) lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Novartis will submit the corresponding data, the analytic and statistical plan used to evaluate the specifications, and any proposed changes to the specifications.
- g. Product Quality Microbiology PMC – To conduct routine bioburden testing (b) (4). 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.
- h. Product Quality Microbiology PMC – To conduct routine bioburden (b) (4). 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.
- i. Product Quality Microbiology PMC – To conduct routine bioburden and endotoxin testing (b) (4). Routine testing will be implemented for the 2015 manufacturing campaign.
- j. Product Quality Microbiology PMC – 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.
- k. Product Quality Microbiology PMC – To evaluate feasibility of (b) (4) secukinumab drug substance and update drug substance specification (b) (4).

6. Review Plans – 5 minutes

- The Office of Compliance has given an overall recommendation of acceptable for the manufacturing sites.
- The Office of Scientific Investigation (OSI) inspection results are complete and appear adequate in support of the respective indication.
- We plan to take an official action in accordance with the PDUFA goal dates.

7. Wrap-up and Action Items – 5 minutes

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

/s/  
-----

TATIANA OUSSOVA  
09/29/2014