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APPLICATION NUMBER:

125504Orig1s000

OTHER REVIEW(S)

Division of Epidemiology I

Date: January 20, 2015

Reviewer(s): Carolyn McCloskey, MD, MPH, Epidemiologist

Team Leader Sukhminder K Sandhu, PhD, MPH, MS, Epidemiology Team Leader

Division Director Simone P Pinheiro, ScD, MSc, Associate Director

Drug Name(s): Cosentyx (secukinumab)

Subject: PMR Language for Long-Term Study of Malignancies

Application Type/Number: BLA 125504 (New Molecular Entity BLA)

Applicant/sponsor: Novartis Pharmaceuticals Corporation

OSE RCM #: 2014-1918

On January 15, 2015, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Epidemiology-1 (DEPI-1) review the sponsor's revised PMR language for Cosentyx (secukinumab). In the revised version, the proposed language changed follow-up time from ^(b)₍₄₎ to 8 years and added an interim study report submission date of June 2027:

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: Mar 2015
Interim Study Report Submission: Jun 2027
Study Completion: Jun 2029
Final Report Submission: Jun 2030

DEPI agrees with the above sponsor proposed PMR language and has no further comments at this time. .

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/s/

CAROLYN A MCCLOSKEY
01/20/2015

SUKHMINDER K SANDHU
01/20/2015

SIMONE P PINHEIRO
01/20/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # BLA 125504
Product Name: COSENTYX (secukinumab)

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.

PMR Schedule Milestones:	Protocol Submission:	<u>03/31/2015</u>
	Interim Study Report Submission:	<u>06/30/2027</u>
	Study Completion:	<u>06/30/2029</u>
	Final Report Submission:	<u>06/30/2030</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a theoretical concern that secukinumab, due to its immunosuppressive effect, may increase the risk of malignancy. The clinical trials were not of sufficient duration to address safety outcomes with a long latency, such as malignancy. Long term data in a large number of patients in a real world setting are needed to provide an assessment of this potential safety signal.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There is a theoretical concern that this new biologic product may increase the risk of malignancies due to immunosuppression.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The recommended study is a 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug

- There is not enough existing information to assess these risks
 - Information cannot be gained through a different kind of investigation
 - The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
 - The trial will emphasize risk minimization for participants as the protocol is developed
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MATTHEW E WHITE
01/20/2015

AMY G EGAN
01/20/2015

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The required trial is an efficacy/safety trial in pediatric patients 6 to 17 years of age with psoriasis.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

MATTHEW E WHITE
01/15/2015

TATIANA OUSSOVA
01/15/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125504
Product Name: Cosentyx (secukinumab)

PMC #1 Description: 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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 12/31/2018
Other: _____

PMC #2 Description: 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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 12/31/2019
Other: _____

PMC #3 Description: 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.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 12/31/2017
Other: _____

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**

• **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

The Drug Substance and Drug Product (vial and prefilled syringe) release and shelf-life specifications approved under BLA are sufficient to ensure adequate quality and safety of secukinumab for the initial marketed product. Additional manufacturing experience gained post licensure can facilitate improved specifications.

2. Describe the particular review issue and the goal of the study.

The Drug Substance and Drug Product (vial and prefilled syringe) release and shelf-life specifications are based on clinical and manufacturing experience provided in the BLA and assessed during the BLA review; however, the number of lots to date do not allow for a robust statistical analysis of the data. Some specifications have a statistical component that should be reassessed when a sufficient number of marketed product lots have been released.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues

Other

Describe the agreed-upon study:

Statistical analysis of release data acquired following manufacture of additional commercial lots

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MATTHEW E WHITE
01/13/2015

TATIANA OUSSOVA
01/14/2015

The recommended trial is to evaluate long-term safety for events which occur infrequently and/or have long latency.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a continuation of currently ongoing long-term efficacy and safety studies to collect additional data on long-term safety.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Long-term extension trials which are ongoing will provide additional safety information
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

MATTHEW E WHITE
01/13/2015

TATIANA OUSSOVA
01/14/2015

The recommended trial is to evaluate long-term safety for events which occur infrequently and/or have long latency.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

This is a continuation of currently ongoing long-term efficacy and safety studies to collect additional data on long-term safety.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
Long-term extension trials which are ongoing will provide additional safety information
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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/s/

MATTHEW E WHITE
01/13/2015

TATIANA OUSSOVA
01/14/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125504
Product Name: Secukinumab

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

PMC Schedule Milestones:

Protocol Submission:	11/2015
Trial Completion:	07/2022
Final Report Submission:	07/2023
Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

We recommend this as a PMC study as the efficacy and safety for secukinumab have been demonstrated in psoriasis patients with the recommended dose. The proposed PMC study will explore the possibility of further improving the therapeutic effect in a subpopulation (subjects with body weight ≥ 90 kg).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The recommended PMC study is based on the lower observed clinical response rates (by approximately 10% with respect to both PASI 75 and IGA 0/1) in subjects with body weight ≥ 90 kg than those in subjects with body weight < 90 kg at the recommended 300 mg dose where no safety concerns were observed. The lower response rate is in part due to lower exposures in subjects with body weight ≥ 90 kg compared to that in subjects with body weight < 90 kg. Simulations with the population PK model indicate that the secukinumab dose of 450 mg administered to subjects with body weight ≥ 90 kg would achieve a similar exposure as the recommended 300 mg dose in subjects with body weight < 90 kg.

The primary goal of the recommended study is to evaluate whether a higher dose (e.g., 450 mg) of secukinumab would achieve better efficacy (or treatment responses) with acceptable safety profile in psoriasis subjects with higher body weight (e.g., ≥ 90 kg) compared to the recommended 300 mg dose. A secondary goal for this study can be added to evaluate whether dose escalation from 300 mg to 450 mg would benefit patients who do not initially respond to the 300 mg dose regimen.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The recommended study is an efficacy/safety trial in a subpopulation of the indicated patient population, i.e., psoriasis subjects with higher body weight (e.g., ≥ 90 kg).

The recommended study should assess both the efficacy and safety of secukinumab in both the induction treatment period (i.e., 12 weeks) as well as during continued treatment. If the study includes a 300 mg comparator arm, non-responders and partial responders on 300 mg at week 12 should be given an option to increase the dosage to 450 mg to evaluate dose escalation in this population. Pharmacokinetic measurements should be conducted to inform exposure-response analysis. We also recommend collection of samples for immunogenicity testing and analyses to assess the impact of immunogenicity on safety, pharmacokinetics, and efficacy. The protocol should be agreed upon by the Agency prior to the initiation of the trial.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MATTHEW E WHITE
01/13/2015

TATIANA OUSSOVA
01/14/2015

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review microbiologist (BMAB) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 125504
 Product Name: Cosentyx (secukinumab)

PMC #1 Description: Conduct routine bioburden testing (b) (4)
 (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.

PMC Schedule Milestones:

Final Protocol Submission:	_____
Study/Trial Completion:	_____
Final Report Submission (method qualification report):	12/31/2015
Other: Evidence of implementation of test	8/31/2016

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDAAA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

Bioburden testing (b) (4) will be conducted to monitor microbial quality of the (b) (4). However, samples for qualification of the bioburden test will not be available until the 2015 campaign. The risk of contaminated samples prior to implementation of the bioburden testing is deemed low because several (b) (4) (b) (4)

2. Describe the particular review issue and the goal of the study.

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

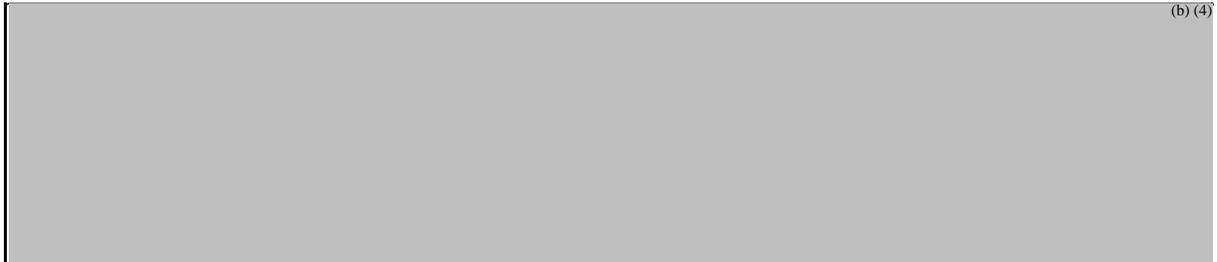
(signature line for BLAs only)

PMC #2 Description: 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.

PMC Schedule Milestones:	Final Protocol Submission:	_____
	Study/Trial Completion:	_____
	Final Report Submission (method qualification report) :	12/31/2015
	Other: Evidence of implementation of test	8/31/2016

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

 (b) (4)

2. Describe the particular review issue and the goal of the study.

 (b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency

- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by BMAB Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMC #3 Description: Conduct routine bioburden and endotoxin testing (b) (4)
Routine testing will be implemented for the 2015 manufacturing campaign.

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: _____
Other: Evidence of implementation of test 3/31/2015

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

(b) (4)
In addition, bioburden testing will be implemented in the next manufacturing campaign.

2. Describe the particular review issue and the goal of the study.

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization

- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

This PMC does not include a study but only testing implementation.

5. To be completed by BMAB Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMC #4 Description: 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

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: 6/30/2016
Other: _____

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

(b) (4)

2. Describe the particular review issue and the goal of the study.

(b) (4)

The proposed study will include microbial quality results (bioburden and endotoxin) from two validation lots of (b) (4) . (b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization

- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The study will include protocol and microbial quality results (bioburden and endotoxin) for the maximum hold time validation of two lots for [REDACTED] (b) (4)
[REDACTED] The validation will be conducted during the 2015 and 2016 production campaigns.

5. To be completed by BMAB Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMC #5 Description: Evaluate feasibility of (b) (4)
secukinumab drug substance and update drug substance specification (b) (4)

PMC Schedule Milestones: Final Protocol Submission: _____
Study/Trial Completion: _____
Final Report Submission: _____
Other: Report of the evaluation conducted 3/31/2015

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

(b) (4)

2. Describe the particular review issue and the goal of the study.

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization

- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

(b) (4)

5. To be completed by BMAB Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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/s/

MATTHEW E WHITE
01/14/2015

TATIANA OUSSOVA
01/14/2015

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

BLA # 125504
Product Name: Secukinumab

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

PMC Schedule Milestones:

Final Protocol Submission:	<u>04/30/2015</u>
Trial Completion:	<u>11/30/2015</u>
Final Report Submission:	<u>5/31/2016</u>
Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

We recommend this as a PMC study as the efficacy and safety for secukinumab have been demonstrated in psoriasis patients. The potential drug-drug interaction between secukinumab and CYP substrates may have impact on the safe and effective use of other concomitant CYP substrates, not the safe or effective use of secukinumab itself.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The recommended drug-drug interaction (DDI) study is based on the current understanding that subjects with psoriasis have elevated levels of proinflammatory cytokines which can suppress the expression of some CYP enzymes and the CYP enzyme expression could be normalized upon the disease improvement following biological treatment. As a result, the exposure of CYP substrates could be reduced when the psoriasis disease condition is improved and the proinflammatory cytokines are normalized. One potential impact of the DDI is the loss of efficacy of the concomitant small molecule CYP substrate drugs which psoriasis patients take.

The goal of the DDI clinical trial is to evaluate the impact of secukinumab treatment on the exposure of CYP substrates in psoriasis patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Because the nature of the drug-drug interaction (DDI) study involves the psoriasis disease conditions (i.e., associated with elevated proinflammatory cytokines and suppressed CYP activity) and the treatment responses (i.e., associated with normalization of cytokine levels and CYP activity), the DDI study needs to be conducted in the indicated patient population. Healthy subjects would not be an appropriate population for the recommended DDI study.

Because the extent of the DDI may differ between responders and non-responders to secukinumab treatment, we recommend the DDI be evaluated in a clinical trial where clinical efficacy data could be obtained to distinguish the responders from the non-responders. Inclusion of pharmacodynamic measurements of cytokine levels in addition to the clinical efficacy would be useful to the data interpretation.

The approved dosing regimen for secukinumab would be appropriate for the DDI study.

Multiple CYP substrate drugs may need to be evaluated in the DDI study because of the complexity of the cytokine network involved in psoriasis disease condition and the disease improvement may have impact on multiple CYP enzymes. Therefore, the selection of appropriate CYP substrate drugs is important and we recommend a cocktail approach.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

Drug interaction study

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

MATTHEW E WHITE
01/13/2015

TATIANA OUSSOVA
01/14/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 10, 2014

To: Kendall Marcus, MD
Director
Division of Dermatology and Dental Products (DDDP)

Through: Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Tara Turner, Pharm.D., MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name), Dosage Form and Route COSENTYX (secukinumab) Injection, for subcutaneous use
COSENTYX (secukinumab) for injection, for subcutaneous use

Application Type/Number: BLA 125504

Applicant: Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On October 24, 2013, Novartis Pharmaceuticals Corporation submitted for the Agency's review an original Biologics License Application (BLA) 125504, for COSENTYX (secukinumab) injection and COSENTYX (secukinumab) for injection. The proposed indication for COSENTYX (secukinumab) injection and COSENTYX (secukinumab) for injection is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dental Products (DDDP) on November 26, 2013 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for COSENTYX (secukinumab) injection, for subcutaneous injection and COSENTYX (secukinumab) for injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA Label and Labeling Review was completed on August 28, 2014.

2 MATERIAL REVIEWED

- Draft COSENTYX (secukinumab) Injection and COSENTYX for injection MG received on October 24, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 30, 2014.
- Draft COSENTYX (secukinumab) Injection, Sensoready PenIFU and COSENTYX (secukinumab) for injection, Prefilled Syringe IFU received on October 24, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 30, 2014.
- Draft COSENTYX (secukinumab) Prescribing Information (PI) received on March 24, 2014 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 30, 2014 and November 26, 2014.
- Approved STELARA (ustekinumab) injection comparator labeling dated March 4, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFUs the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more

accessible for patients with vision loss. We have reformatted the MG and IFUs document using the Verdana font, size 11.

In our collaborative review of the MG and IFUs we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

36 Page(s) of Draft Labeling have been Withheld in Full as
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/s/

SHARON R MILLS
12/10/2014

TARA P TURNER
12/10/2014

BARBARA A FULLER
12/10/2014

OBP Labeling Review



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Division of Monoclonal Antibodies
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date: December 3, 2014

Reviewer: Jibril Abdus-Samad, PharmD
Office of Biotechnology Products

Jibril Abdus-samad -S

Digitally signed by Jibril Abdus-samad -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S
Date: 2014.12.03 09:39:09 -05'00'

Through: Tura Camilli, PhD, Product Quality Reviewer
Division of Monoclonal Antibodies

Tura C. Camilli -S

Digitally signed by Tura C. Camilli -S
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Date: 2014.12.03 17:18:27 -05'00'

Sarah Kennett, PhD, Review Chief
Division of Monoclonal Antibodies

Sarah B. Kennett -S

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Date: 2014.12.03 17:22:15 -05'00'

Application: BLA 125504

Product: Cosentyx (secukinumab)

Applicant: Novartis Pharmaceuticals Corporation

Submission Dates: October 23, 2013 and December 23, 2013

Executive Summary

The container labels and carton labeling for Cosentyx (secukinumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia [8/1/2014 – 11/30/2014 current revision] USP 37/NF 32. The initial labeling deficiencies were identified, mitigated, and resolved. The labels and labeling submitted on November 10, 2014 are acceptable with the exception of the pen label, whose acceptable label was submitted on November 20, 2014.

Background and Summary Description

BLA 125504 Cosentyx (secukinumab) was submitted on October 23, 2013 with a proposed indication for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Cosentyx is supplied in the following dosage forms and strengths

- Injection: 150 mg/mL solution in a single-use prefilled Sensoready® pen
- Injection: 150 mg/mL solution in a single-use prefilled syringe
- For Injection: 150 mg lyophilized powder in a single-use vial

The recommended dose is 300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at week 4. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg. For some patients, a dose of 150 mg may be acceptable.

Materials Reviewed:

1. Sensoready Pen - trade and physician sample
 - Carton Labeling, 2 x 150 mg/mL
 - Carton Labeling, 150 mg/mL
 - Container Label, 150 mg/mL
2. Prefilled Syringe (PFS) - trade and physician sample
 - Outer Carton Labeling, 2 x 150 mg/mL
 - Inner (b) (4) Labeling, 2 x 150 mg/mL
 - Outer Carton Labeling, 150 mg/mL
 - Inner (b) (4) Labeling, 150 mg/mL
 - Syringe Label 150 mg/mL
3. Vial
 - Carton Labeling, 150 mg/vial
 - Container Label, 150 mg/vial

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Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

PFS and Vial Container Labels

Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum;

1. name (expressed either as the proper or common name);
conforms.
2. lot number or other lot identification; *conforms.*
3. name of the manufacturer;

Vial: *Conforms*, but revise to preferred format.

OBP request: Revise the manufacturer information so that the manufacturer appears first, then the US License Number, thus "Novartis, US Lic. No 1244".
Applicant revised as requested.

PFS: does not conform

OBP Request: Revise the manufacturer information to comply with [21 CFR 600.3(t), 21 CFR 610.60(c)]. Thus, the manufacturer information should read as follows:

Mfd by: Novartis
East Hanover NJ 07936
US Lic. No 1244

Applicant revised as requested.

4. for multiple dose containers, the recommended individual dose. *Not applicable.*
5. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label.
Conforms.

Pen Container Label and Inner ^{(b) (4)} Labeling

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label:

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. *Conforms.*

(2) The name, address, and license number of manufacturer; pen does not conform.

OBP Request: Revise the manufacturer information to comply with the definition of manufacturer [21 CFR 600.3(t), 21 CFR 610.60(2)]. For example:

Mfd by: Novartis Pharmaceutical Corp., East Hanover, NJ 07936

US License No. 1244

*at

Novartis Pharma Stein AG, Stein, Switzerland

*Consider deleting this site on the container label to create space for the required and recommended information. This site already appears on the Carton Labeling. *Applicant revised as requested.*

(3) The lot number or other lot identification; *Conforms.*

(4) The expiration date; *Conforms.*

(5) The recommended individual dose, for multiple dose containers. *Not applicable. Single-dose containers.*

(6) The statement: "Rx only" for prescription biologicals. *Conforms.*

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label.

Conforms, MG statement appears on the package/carton labeling.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable.*

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which

bears all the items required for a package label. *Not applicable for Pen.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable.*

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation per CMC visual inspection. *Applicant confirmed.*

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *Conforms.*

C. 21 CFR 201.5 Drugs; adequate directions for use; *Conforms.*

D. 21 CFR 201.6 Drugs; misleading statements; *Conforms.*

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] *Conforms.*

F. 21 CFR 201.15 Drugs; prominence of required label statements; conforms, but OBP recommends revising inner ^{(b) (4)}.

OBP Request: Relocate the information that appears below and to the right of the Rx only statement to the bottom panel to make room for the required information on the PDP (proprietary and proper names, strength, NDC, warning statements). *Applicant revised as requested.*

G. 21 CFR 201.17 Drugs; location of expiration date; *Conforms.*

H. 21 CFR 201.25 Bar code; *Conforms.*

I. 21 CFR 201.50 Statement of identity; *Conforms.*

J. 21 CFR 201.51 Declaration of net quantity of contents;

PFS and Pen conform however OBP recommends revising.

Vial does not conform.

OBP Request: Revise the strength presentation accordingly.

Pens:

150 mg/mL

2 Sensoready Pens

150 mg/mL

1 Sensoready Pen

PFS:

150 mg/mL

2 Prefilled Syringes

150 mg/mL

1 Prefilled Syringe

Applicant's Response: Specifically for the Pen and PFS with quantity of 2, the strength was revised to:

Pen:

150 mg/mL

2 Sensoready Pens

(300 mg dose)

PFS:

150 mg/mL

2 Prefilled Syringes

(300 mg)

Acceptable.

Vial:

Revise the strength presentation from "(b) (4)" to "150 mg/vial". As detailed in your submission, the overfill is adequate and required to ensure that the labeled volume 1 mL (150 mg) can be withdrawn from the vial. There is no significant excess volume of reconstituted solution. Thus, the overfill should not be declared on the labels and labeling. *Applicant revised as requested.*

K. 21 CFR 201.55 Statement of dosage; *Conforms.*

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

II. Carton

A. 21 CFR 610.61 Package Label

a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *Conforms.*

The name, addresses, and license number of manufacturer; does not conform.

OBP Request: Revise the manufacturer information to comply with the definition of manufacturer [21 CFR 600.3(t) and 21 CFR 610.61(b)]. Additionally, list the US License Number on the 356h form. For example:

Manufactured by: Novartis Pharmaceutical Corporation
East Hanover, NJ 07936
US License No. 1244

at
Novartis Pharma Stein AG,
Stein, Switzerland

Product of France
Applicant revised as requested.

b) The lot number or other lot identification; *Conforms.*

c) The expiration date; *Conforms.*

d) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *Conforms.*

e) The number of containers, if more than one; *Conforms.*

f) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable;

- *Sensoready Labeling Conforms.*
- *PFS Labeling Conforms.*

- Vial Labeling does not conform.
OBP Request: Revise the strength presentation from (b) (4) to "150 mg/vial". As detailed in your submission, the overfill is adequate and required to ensure that the labeled volume 1 mL (150 mg) can be withdrawn from the vial. There is no significant excess volume of reconstituted solution. Thus, the overfill should not be declared on the labels and labeling. Applicant revised as requested.

- g) The recommended storage temperature; *conforms*.

- h) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.

- i) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable*.

- j) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.

- k) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.

- l) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

- m) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

- n) The adjuvant, if present; *not applicable*.

- o) The source of the product when a factor in safe administration; *not applicable*.

- p) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

q) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*. However OBP recommends revising to decrease prominence.

OBP Request: Remove the bolding from the statement "No US standard of potency". *Applicant revised as requested.*

r) The statement "Rx only" for prescription biologicals; *conforms*.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Conforms*.

B. 21 CFR 610.62 Proper name; package label; legible type [*Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)*]; **Exempt**, monoclonal antibody product for in vivo use.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases:

"Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. *Not applicable to all labeling*.

E. 21 CFR 610.67 Bar code label requirements

Biological products must comply with the bar code requirements at §201.25 of this chapter; *conforms*.

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label. [See 21 CFR 207.35] *Conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; does not conform

OBP Request: Revise the statement on the PDP that reads
“(b) (4)” Reconstitute with
1 mL of Sterile Water for Injection, USP to obtain a concentration
of 150 mg/mL of secukinumab”. *Applicant revised as requested.*

H. 21 CFR 201.6 Drugs; misleading statements; *Conforms.*

I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence] *conforms.*

J. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms however OBP recommends revising.*



OBP Request: Relocate the graphic away from the proprietary name. As currently presented, the graphic is in close proximity to the proprietary name and can be misinterpreted as part of the proprietary name.

OBP Request: Add the dosage form to appear under the proper name, secukinumab, in the identical font size and style as the proper name on the principal display panel (PDP) and side panels. The pen and prefilled syringe labels and labeling should appear as:

Cosentyx
(secukinumab)
Injection

The vial label and labeling should appear as:

Cosentyx
(secukinumab)
For Injection

Applicant revised as requested.

K. 21 CFR 201.17 Drugs; location of expiration date; *Conforms.*

L. 21 CFR 201.25 Bar code label requirements; *Conforms.*

M. 21 CFR 201.50 Statement of identity; *Conforms.*

N. 21 CFR 201.51 Declaration of net quantity of contents;

PFS and Pen conform however OBP recommends revising

Vial does not conform.

OBP Request: Revise the strength presentation on the PDP and side panels accordingly.

Pens:

150 mg/mL
2 Sensoready Pens

150 mg/mL
1 Sensoready Pen

PFS:

150 mg/mL
2 Prefilled Syringes

150 mg/mL
1 Prefilled Syringe

Applicant's Response: Specifically for the Pen and PFS with quantity of 2, the strength was revised to:

Pen:

150 mg/mL
2 Sensoready Pens
(300 mg dose)

PFS:

150 mg/mL
2 Prefilled Syringes
(300 mg)
Acceptable.

Vial:

Revise the strength presentation from (b) (4) to "150 mg/vial". As detailed in your submission, the overfill is adequate and required to ensure that the labeled volume 1 mL (150 mg) can be withdrawn from the vial. There is no significant excess volume of reconstituted solution. Thus, the overfill should not be declared on the labels and labeling. *Applicant revised as requested.*

O. 21 CFR 201.55 Statement of dosage; *Conforms*.

P. 21 CFR 201.100 Prescription drugs for human use; does not conform.

OBP Requests:

Revise the list the names of the inactive ingredients in alphabetical order in the following format "inactive ingredient (amount)" per United States Pharmacopeia (USP) 37/NF 32 (8/1/2014-11/30/2014), General Chapters: <1091> Labeling of Inactive Ingredients. *Applicant revised as requested.*

Specifically for the Vial Carton, relocate the list of inactive ingredients to the bottom panel to read as follows:

"After reconstitution, each mL contains secukinumab (150 mg), L-histidine/L-histidine hydrochloride monohydrate (4.656 mg), polysorbate 80 (0.6 mg/mL), Sterile Water for Injections, USP (1 mL) and sucrose (92.43 mg/mL)."

Note the deletion of the trailing zero (revise 1.0 mL to 1 mL and 0.60 mg/mL to 0.6 mg/mL). *Applicant revised as requested.*

Revise the statement

(b) (4)

(b) (4)" to read "See package insert for dosage, reconstitution, and administration information." Note "reconstitution" replaces "(b) (4)".

Applicant revised as requested.

CDER Labeling Recommendations

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences. For all these concerns, the Applicant's response was acceptable.

A. General Comment for all Container Labels

1. Indicate how the label is affixed to the vial, prefilled syringe, and prefilled Sensoready Pen as well as where the visual area of inspection is located per 21 CFR 610.60(e).

B. Prefilled Syringe Container Label, 150 mg/mL

1. We consider the PFS Label a partial label [21 CFR 610.60(c)] due their small size. Our recommendations below aim to provide the required and most important on the label and remove less important information to provide more white space and readability.

2. Delete the storage and handling statements information to lessen crowding, improve spacing and readability of the label. The storage information is not required on partial labels per 21 CFR 610.60(c). The storage and handling information already appears on both the Outer and Inner ^{(b) (4)} Labeling.
3. Clarify the significance of the code "804514 US" that appears on the top right of the PDP. Consider relocating this information toward the bottom of the labeling, away from the required and recommended information on the carton labeling.

Novartis response: This code is an internal Novartis component control number and used for version control, inventory purposes and tracking. This number is also used to identify components in the Current Labeling and Summary Changes in the NDC Annual Report.
Acceptable.

4. Revise the statement "Single Use" to read "Single Use Only".

C. Vial Carton Labeling

1. Revise the statement "Single-Use Vial" on the PDP to read "Single-Use Vial, Discard Unused Portion" to appear below the statement "For Subcutaneous Use Only". Thus the PDP should appear as

Cosentyx
(secukinumab)
For Injection

150 mg/vial

For Subcutaneous Use Only
Single-Use Vial, Discard Unused Portion

2. Revise the side panels to appear as:

Cosentyx
(secukinumab)
For Injection

150 mg/vial

For Subcutaneous Use Only

3. Revise the diluent statements that read "sterile water for injection" to read "Sterile Water for Injection, USP".

4. Revise the use of bolding on the bottom panel to bring attention to the most important information and improve readability. The large amount of bolded text decreases readability. Consider bolding subject headings such as Storage, Reconstitution, and After preparation.

D. Vial Container Label

1. Revise the storage information to read, "Store vial refrigerated 2°C-8°C (36°F-46°F) in original carton to protect from light."
2. Comment on if there is any text on the ferrule and cap overseal to comply with a revised USP standard [USPC Official 8/1/2014 – 11/30/2014, USP 37/NF 32, <1> Injections/General Requirements.] that went into effect on December 1, 2010. We refer you to the following address:
http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/genChapter1Labeling.pdf

Conclusions

The initial labeling deficiencies were identified, mitigated, and resolved. The labels and labeling submitted on November 10, 2014 are acceptable with the exception of the pen container label, whose acceptable label was submitted on November 20, 2014.

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 14, 2014

To: Matthew White
Regulatory Project Manager
Division of Dermatology and Dental Products (DDDP)

From: Tara Turner, Pharm.D., MPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Through: Melinda McLawhorn, PharmD, BCPS
Regulatory Review Officer, OPDP

CC: Adora Ndu, Pharm.D., Team Leader, OPDP

Subject: **BLA 125504**
COSENTYX™ (secukinumab) Injection, for subcutaneous use
COSENTYX™ (secukinumab) for Injection, for subcutaneous use

On November 26, 2013, DDDP consulted OPDP to review the draft Package Insert labeling (PI), carton and container labeling, Medication Guide (MG) and Instructions for Use (IFU) for COSENTYX™ (secukinumab) Injection, for subcutaneous use and COSENTYX™ (secukinumab) for Injection, for subcutaneous use (Cosentyx) for the original BLA submission.

OPDP reviewed the proposed substantially complete version of the PI provided by DDDP via e-mail on September 30, 2014. OPDP also reviewed the original carton and container labeling submitted to the electronic document room by the sponsor on October 24, 2013. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the MG and IFU for Cosentyx under separate cover. OPDP's comments on the draft PI and carton and container labeling are provided below. We note that the dosing and administration of Cosentyx will be discussed at an upcoming advisory committee meeting. OPDP would appreciate the opportunity to comment on revised labeling after this meeting.

Thank you for your consult. If you have any questions about OPDP's comments, please contact Tara Turner at 6-2166 or at Tara.Turner@fda.hhs.gov.

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/s/

TARA P TURNER
10/14/2014

STUDY ENDPOINT CONSULT REVIEW

STUDY ENDPOINTS TRACKING NUMBER 2014-005
BLA NUMBER 125504

LETTER DATE/SUBMISSION NUMBER eCTD sequence #0000
PDUFA GOAL DATE January 23, 2015
DATE OF CONSULT REQUEST January 9, 2014

REVIEW DIVISION Division of Dermatology and Dental
Products (DDDP)
MEDICAL REVIEWER Amy Voitach
REVIEW DIVISION PM Mathew White

STUDY ENDPOINTS REVIEWER Yasmin Choudhry
ASSOCIATE DIRECTOR (ACTING), Elektra Papadopoulos
STUDY ENDPOINTS

REVIEW COMPLETION DATE September 8, 2014

ESTABLISHED NAME Secukinumab
TRADE NAME Cosentyx
SPONSOR/APPLICANT Novartis Pharmaceuticals Corporation

CLINICAL OUTCOME ASSESSMENT Patient Reported Outcome
TYPE

ENDPOINT(S) CONCEPT(S) Psoriasis-related itching, pain and
scaling

MEASURE Psoriasis Symptom Diary

INDICATION For the treatment of moderate to
severe plaque psoriasis in adult
patients who are candidates for
systemic therapy or photography

INTENDED POPULATION Adult patients with moderate to severe
chronic plaque psoriasis

Study Endpoints Team Review

Yasmin Choudhry, M.D.

BLA 125504

Cosentyx (secukinumab)

Psoriasis Symptom Diary

A. EXECUTIVE SUMMARY

This Study Endpoints review is provided as a response to a request for consultation by the Division of Dermatology and Dental Products (DDDP) regarding BLA 125504 Cosentyx (secukinumab) received on October 24, 2013.

The sponsor developed a new 16-item patient-reported outcome (PRO) measure, the electronic Psoriasis Symptom Diary for the measurement of **itching, pain and scaling** in patients with chronic plaque psoriasis for use as secondary endpoint in phase 3 clinical trials. The 16 items of the diary evaluate signs and symptoms, patient-reported bother, and psoriasis-related daily impacts.

The proposed PRO labeling claim is *improvements in itching, pain, and scaling at week 12 compared with placebo* based on a subset of Psoriasis Symptoms Diary's items (items 1, 9, and 11), which were pre-specified as a secondary study endpoint. While the entire instrument was administered during the trial, the sponsor is not seeking a claim based on the overall score of the Psoriasis Diary.

This review concludes that the sponsor has provided sufficient evidence to support the validity and reliability of these three items to support proposed labeling claim of improvements in itching, pain, and scaling provided that the clinical trial data are clinically meaningful and statistically robust as determined by the clinical and statistical review staff.

We generally recommend avoiding the use of the term “(b) (4)” as a blanket statement, because it does not clarify the context in which an instrument is considered valid for use. Therefore, if the labeling claim is granted, we recommend that the term “(b) (4)” be removed from the labeling statement. We believe that evaluation of cumulative distribution function curves may also be useful; as these curves show the entire distribution of responses for treatment and control group to aid in interpretation of clinically meaningful change as described in the FDA Guidance for Industry: *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (2009)*.

B. STUDY ENDPOINT REVIEW

Materials Reviewed:

- Novartis' PRO Evidence Dossier (dated August 21, 2013) received October 24, 2013
- FDA communications/Advice Letters dated August 24, & July 12, 2011

Study Endpoints Team Review

Yasmin Choudhry, M.D.

BLA 125504

Cosentyx (secukinumab)

Psoriasis Symptom Diary

- Study Endpoints Reviews of IND 100418 completed June 22, 2009; March 2, & December 17, 2010; and May 13, and August 24, 2011

Background:

Novartis is developing secukinumab, a recombinant high-affinity human monoclonal Interleukin-17A (IL-17A) antibody of the IgG1/ κ -class, for the treatment of moderate to severe (b) (4) plaque psoriasis. The May 13, 2011 SEALD review of the Psoriasis Symptom Diary concluded that:

- To support a claim of treatment of symptoms, a well-defined and reliable assessment of severity of the core symptoms of psoriasis in the intended clinical trial target population will be required.
- The symptom impact assessment (i.e., items 2, 4, 6, 8, 10, 12, 13, 14, 15, and 16) are less likely to support claims of treatment benefit as compared with the core symptoms of the disease. In addition, inclusion of the symptom impact items and the core symptom items in a single overall score will tend to increase the variability of the measure and might jeopardize the interpretation of the treatment effect on the core symptoms of disease.
- We recommend that the sponsor develop a separate (symptom and impact) conceptual framework and score for the proposed items. A complete PRO dossier submission will be needed to review the content validity and other measurement properties of the final version of the instrument in accordance with the 2009 PRO Guidance for Industry.

The PRO dossier received October 24, 2013 is the subject of this review.

1 CONTEXT OF USE

1.1 Target Study Population and Clinical Setting

The target population is adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy.

1.2 Clinical Trial Design

The Psoriasis Symptom Diary was studied in two randomized, double-blind, placebo-controlled, multicenter phase 3 secukinumab clinical trials (Study CAIN457A2302 and CAIN457A2303).

The key inclusion criteria were as follows:

- Adults, at least 18 years of age;
- Diagnosis of chronic plaque-type psoriasis for at least 6 months prior to randomization;

Study Endpoints Team Review

Yasmin Choudhry, M.D.

BLA 125504

Cosentyx (secukinumab)

Psoriasis Symptom Diary

- Moderate to severe psoriasis defined as PASI score of minimally 12, an investigator's global assessment (IGA mod 2011) of at least 3 on a scale from 0-4 and a total BSA of minimally 10%;
- Candidate for systemic therapy, defined as having chronic plaque-type psoriasis considered inadequately controlled by topical treatment and/or phototherapy and/or previous systemic therapy.

Patients with forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis) and drug-induced psoriasis were excluded.

1.3 Endpoint Positioning

In the secukinumab Phase 3 clinical trials (Study CAIN457A2302 and Study CAIN457A2303), the Psoriasis Symptoms Diary's items (items 1, 9, and 11) were used as secondary study endpoints. The primary efficacy endpoints were based on clinician-reported outcome measures (PASI score and an investigator global assessment).

1.4 Labeling or promotional claim(s) based on the COA

The Psoriasis Symptom Diary-related proposed labeling is as follows: (b) (4)
improvements in signs and symptoms related to itching, pain, and scaling at week 12 compared to placebo (b) (4).

Reviewer comment: The sponsor's proposed labeling claim for itching, pain and scaling (measured by items 1, 9, and 11) matches the concept measured in pre-specified analysis and is acceptable. However, we recommend that the term "(b) (4)" be removed from the labeling statement above. The term "(b) (4)" is not appropriate in this context.

2 CONCEPT OF INTEREST AND CONCEPTUAL FRAMEWORK

The conceptual framework is presented below in Table 5 (page 39/1528) of the dossier:

Study Endpoints Team Review

Yasmin Choudhry, M.D.

BLA 125504

Cosentyx (secukinumab)

Psoriasis Symptom Diary

Table 5. Conceptual Framework for the Psoriasis Symptom Diary

Psoriasis Symptom Diary Item	Concept Assessed
1. Overall, how <u>severe</u> was your psoriasis-related itching over the past 24 hours?	Psoriasis-related itching
2. Overall, how <u>bothered</u> were you by your psoriasis-related itching over the past 24 hours?	Bother due to psoriasis-related itching
3. Overall, how <u>severe</u> was your psoriasis-related stinging over the past 24 hours?	Psoriasis-related stinging
4. Overall, how <u>bothered</u> were you by your psoriasis-related stinging over the past 24 hours?	Bother due to psoriasis-related stinging
5. Overall, how <u>severe</u> was your psoriasis-related burning over the past 24 hours?	Psoriasis-related burning
6. Overall, how <u>bothered</u> were you by your psoriasis-related burning over the past 24 hours?	Bother due to psoriasis-related burning
7. Overall, how <u>severe</u> was the pain from your psoriasis-affected skin cracking over the past 24 hours?	Psoriasis-related pain from skin cracking
8. Overall, how <u>bothered</u> were you by the pain from your psoriasis-affected skin cracking over the past 24 hours?	Bother due to psoriasis-related pain from skin cracking

Study Endpoints Team Review

Yasmin Choudhry, M.D.

BLA 125504

Cosentyx (secukinumab)

Psoriasis Symptom Diary

Psoriasis Symptom Diary Item	Concept Assessed
9. Overall, how <u>severe</u> was your psoriasis-related pain over the past 24 hours?	Psoriasis-related pain
10. Overall, how <u>bothered</u> were you by your psoriasis-related pain over the past 24 hours?	Bother due to psoriasis-related pain
11. Overall, how <u>severe</u> was your psoriasis scaling over the past 24 hours?	Psoriasis-related scaling
12. Overall, how <u>bothered</u> were you by your psoriasis scaling over the past 24 hours?	Bother due to psoriasis-related scaling
13. Overall, how noticeable did you think the color of your psoriasis-affected skin was over the past 24 hours?	Psoriasis-related skin color
14. Overall, how much did you try to hide your psoriasis-affected skin over the past 24 hours?	Bother due to psoriasis-related skin color
15. Overall, how much did your psoriasis cause you to avoid activities with other people over the past 24 hours?	Avoidance of Activities with other People due to Psoriasis
16. Overall, how embarrassed were you because of your psoriasis over the past 24 hours?	Embarrassment over Appearance of Psoriasis

Reviewer comment: While the Psoriasis Symptom Diary includes psoriasis signs (skin color, scaling, and cracking), symptoms (itching, stinging, pain, burning) and disease impact (embarrassment etc.), the sponsor is only pursuing a label claim for the three most-reported symptoms (itching, pain, scaling) based on items 1, 9, and 11. The proposed labeling claim using the three items is appropriate if the effect of the drug on this endpoint is found to be clinically meaningful and statistically significant.

Study Endpoints Team Review

Yasmin Choudhry, M.D.

BLA 125504

Cosentyx (secukinumab)

Psoriasis Symptom Diary

3 CLINICAL OUTCOME ASSESSMENT (COA) MEASURE(S)

The proposed electronic Psoriasis Symptom Diary contains 16 items. A total of seven items evaluate signs and symptoms of plaque psoriasis (items 1, 3, 5, 7, 9, 11, 13) and additional seven items evaluate patient-reported bother associated with the experience of those signs and symptoms (items 2, 4, 6, 8, 10, 12, and 14). The last two items of the Psoriasis Symptom Diary evaluate psoriasis-related daily impacts (items 15 and 16).

The items # 1, #9, and #11 (severity of itching, pain and scaling) were proposed to support labeling goals for the secukinumab development program. See Attachment A: Psoriasis Symptom Diary.

Each of the 16 Psoriasis Symptom Diary items was scored as weekly averages up to week 12. A weekly average is the sum of the scored item over the course of the study week divided by the number of days on which the item was completed. For the Psoriasis Symptom Diary items, 4 completed days are necessary to derive a weekly score (1-3 missed days, consecutive or nonconsecutive, are allowed). Cases for which a weekly score cannot be calculated (less than 4 completed days) are set to missing and cannot be included in the analysis.

The response options included are based on an 11-point numeric rating scale ranging from 0 to 10. The symptom severity items ranged from 0 (None) to 10 (as bad as you can imagine). Likewise the items on bother ranged from 0 (No bother at all) to 10 (bother as bad as you can imagine).

The recall option chosen for the Psoriasis Symptom Diary was 24 hours.

Reviewer comment: We agree with the measurement of the selected items for the proposed labeling claim and with the 24-hour recall period for reporting symptoms.

4 CONTENT VALIDITY

The evidence of content validity for the electronic Psoriasis Symptom Diary provided by the sponsor is as follows:

Expert Consensus: The sponsor's expert consensus was based on:

- Literature review of the published observational studies, clinical trials, psoriasis assessment, and instrument development and validation reports from the MEDLINE and relevant websites.
- Opinion of two dermatology clinical experts.
- FDA's 2009 final PRO guidance.

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Concept Elicitation Interviews: Open-ended and in-depth concept elicitation interviews were conducted in 29 patients with chronic moderate to severe psoriasis recruited from clinics from 2 US sites. The target sample was comparable to the target population for the Novartis clinical trials (see I inclusion criteria in Section 1.2 of this review); the average age of patients was 65 years (range 32-75), the number of males and females was equal, more than 35% had an educational level of high school and over, and majority of patients were Caucasian. Each patient completed an interview by 2 interviewers with the help of a Concept Elicitation Interview Guide; and each concept was given a code in using *ATLAS.ti* software; the results of the coding between the two interviewers were compared for consistency and to ensure detailed transparency in the identification of all relevant concepts/codes used for that content.

As shown in Table 6 below taken from page 43/1528 of the dossier, the concepts evaluated by the Psoriasis Symptom Diary were supported and substantiated from all three sources of information:

Table 6. Concept Justification Matrix for Psoriasis

Concept	Empirical Data	Expert Input	Patient Interviews
Psoriasis-related itching	YES	YES	YES
Psoriasis-related stinging and burning	YES	YES	YES
Psoriasis-related cracking	YES	YES	YES
Psoriasis-related pain	YES	YES	YES
Psoriasis-related scaling	YES	YES	YES
Psoriasis-related skin color	YES	YES	YES

Note: Shaded rows reflect concepts related to labeling objectives in CAIN457A2302 and CAIN457A2303.

The demographics of the patients are shown in the table below taken from page 46/1528 of the dossier:

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Table 7. Demographic Information (Concept Elicitation)

Characteristic	Total (N = 29)
Age (years):	
Mean (SD)	65 (9)
Range	32-75
Gender, n (%)	
Male	15 (52%)
Female	14 (48%)
Education, n (%)	
Elementary school	1 (3%)
High school	10 (35%)
College	13 (45%)
Graduate/professional school	5 (17%)
Employment status, n (%)	
Full-time	16 (55%)
Part-time	4 (14%)
Retired	7 (24%)
Not employed	2 (7%)
Ethnicity, n (%)	
White	24 (83%)
Black/African American	2 (7%)
Hispanic or Latino	1 (3%)
American Indian	1 (3%)
Asian/Pacific Islander	1 (3%)
PASI score	
Mean (SD)	18.5 (10.1)
BSA score	
Mean (SD)	16.3% (8.4)
IGA score	
Mean (SD)	3.3 (0.6)

BSA = body surface area; IGA = Investigator Global Assessment; PASI = Psoriasis Area and Severity Index; SD = standard deviation.

The psoriasis symptoms identified in the interviews were evaluated against two primary criteria: 1) the number and proportion of patients who mentioned experiencing a concept, 2) the frequency and proportion at which a concept was mentioned across interviews. Additionally, symptom-level concepts were evaluated by the degree to which the symptoms reportedly "bother" the patient. The patient interview data support the seven symptoms of psoriasis as specified in the conceptual model (including those related to labeling objectives), which were also identified in the expert interviews and the empirical literature. Each concept specified in the conceptual model (i.e., those measured by the Psoriasis Symptom Diary) was reported by at least 70% of all the interviewed patients and each was discussed at least 10% of the time relative to all the number of times any symptom-level concept was discussed.

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Achievement of saturation of symptom concepts was demonstrated as shown in the table below taken from page 47/1528 of the Evidence Dossier:

Table 8. Summary Saturation Matrix of Psoriasis Symptom Concepts

Symptom-level Concepts	Cohort 1 n = 10	Cohort 2 n = 9	Cohort 3 n = 10
Number of new concepts coded	58	12	0
Percentage of total concepts coded (N = 70)	83%	17%	0%

A summary of symptom frequency is shown in the table below taken from page 49/1528 of the dossier:

Table 9. Summary of Symptom Frequency

Domain: Symptom	Number of Symptom Mentions of Concepts	Percentage of Total Symptom Mentions (n = 929) ^a	Number of Individuals Contributing to the Symptom Domain (n = 29)	Percentage of Individuals (of total of 29)
Appearance	148	16%	29	100%
Itchy	131	14%	29	100%
Stiffness/Tightness	20	2%	15	52%
Plaque-Related Pain	322	35% ^b	29	100%
Scaling ^c	119	13%	21	72%
Flaking	61	7%	23	79%
Thickness	24	3%	12	41%
Joint Pain/Arthritis	31	3%	18	62%
Other Symptoms	134	14%	29	100%

^a A symptom "mention" or "expression" indicates the concept was coded (from the transcription) as a symptom. The total n reflects all the symptoms mentioned during the interviews (929) and not just those characterized in the conceptual model.

^b During concept elicitation interviews, psoriasis pain-related concepts (stinging, burning, cracking, and pain) were summarized under a single category (i.e., 35% of all symptom-level mentions across interviews were about psoriasis-related pain including overall pain and specific pain descriptors [e.g., stinging and burning]).

^c During the concept elicitation interviews, scaling and flaking were conceptualized as unique concepts. Subsequent cognitive interviewing data suggested that patients do not distinguish between these two concepts. This data reflects only mentions and inquires about "scaling" (which was the word of choice among plaque psoriasis patients) and these data may be a conservative estimate with respect to the importance and relevance of the concept.

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The following table, taken from page 50/1528, shows the bother rating for psoriasis symptoms:

Table 10. Bother Rating for Psoriasis Symptoms

Symptom of Psoriasis From Concept Elicitation Interviews	Individual Who Mentioned Symptoms, n	Bother Rating, mean ^a (SD)
Itchy (Itch, itches)	27	6.6 (2.7)
Sore, Painful (Cracking pain, hurt, hurts/ tender, pain, painful, painful when cracks, scalded/hurt, tender to touch, sore, tender)	17	7.3 (2.1)
Uncomfortable (Uncomfortable, uncomfortable behind the ears)	6	7.3 (3.2)
Stinging (Stinging, bee stinging)	8	8.0 (2.2)
Hot (Hot)	3	4.0 (1.7)
Redness (Red, red spots, redness, redness with lotion, redness/grayness/darkness, redness/pink skin, spots, when others see it)	22	6.7 (3.4)
Scales on the skin (Dry patches, more scale patches/scaliness, plaques, scales on the skin, scaling)	19	7.2 (3.1)
Leaving flakes (Chaffing/dry skin, dandruff, dead skins, flake off, flaking, leaving flakes, peeling, peeling flakes, skin, snowflakes)	22	7.5 (2.3)
Tightness (Tightness, tightness skin)	6	7.5 (3.0)
Stiffness (Stiffness, stiffness knee, swelling, swelling ears)	7	7.7 (2.2)
Joint aches (Arthritis, joint aches, joint pain, joints sore, sore joints)	9	7.4 (2.7)

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Inter-rater agreement: Interview transcripts were reviewed for patient expressions of concepts related to the study objectives, and each concept was assigned a unique code using *ATLAS.ti* software. In order to establish the reliability of coding, two raters reviewed and coded four interview transcripts. Inter-rater agreement was established in two ways: 1) inter-rater agreement was defined as the percentage of transcription text that was mutually seen as "codable" (i.e., should be assigned a symptom or impact code and subject to analysis), and 2) inter-rater agreement was defined as the percentage of coded text that was assigned the same code by both raters.

For the four transcripts that were reviewed for inter-rater agreement, the raters achieved 80% agreement in the identification of occurrences of text that should be coded and each of the raters labeled the concepts with the same specific code 97% of the time.

Reviewer Comment: The interview data support the 7 symptoms of psoriasis (conceptual model) including those for which the sponsor seeks the labeling claim i.e., itching, scaling and pain; each of these concepts was reported by at least 70% of all the interviewed patients and each was discussed at least 10% of the time relative to all the number of times any symptom-level concept was discussed. The interviews also demonstrated the importance of the disease impact "bothersome" in patients with psoriasis.

In the table 8 above, the sponsor demonstrated symptom concept saturation after interviewing 3 cohorts of patients. The sponsor's tables (# 9 & 10) above show that of the 29 individuals, itching was reported by 27 with a bothersome rating of 6.6(2.7); pain was reported by 17 individuals with a bothersome rating of 7.3(2.1); and scaling by 19 individuals with a bothersome rating of 7.2(3.1).

We find this data sufficient to support the labeling claim.

Cognitive Debriefing Interviews:

The cognitive debriefing interviews were designed to meet three objectives:

- Assess patient comprehension of the concepts presented in the preliminary items
- Identify any difficulties with language, format, instructions, or response options
- Inform appropriate revisions to the items

The methods and procedures used for the cognitive interviews are similar to those used in the concept elicitation interviews.

Sixteen patients (recruited from two private clinics in the US) evaluated the instrument and provided feedback on the instructions, wording of the items, format of the instrument, and the response options of each item. Areas of difficulty were then highlighted and changes were made until patients reported comprehension. This process was repeated until an optimal level of

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comprehension was achieved by patients. From there, the next version of the Psoriasis Symptom Diary was created. The development and iterative modification of the items, response options, and instructions that comprise the Psoriasis Symptom Diary were recorded and tracked in an Item Tracking Matrix.

The sponsor provided two examples of how the cognitive interviews contributed to revisions to the draft items:

1. Original items included the term "plaque-related." Because patients did not respond well to that phrase, it was replaced with "psoriasis-related" as this was predominant patient language and more meaningful to them.
2. Patients indicated that they do not differentiate between flaking and scaling and, therefore, saw the two unique items from the original set of items as redundant. Moreover, because "scaling" was the predominate language, the question from the original set of items that referenced "flaking" was eliminated.

Reviewer Comment: The sponsor has demonstrated that for most symptoms, patients confirmed that the severity of the symptom was the most relevant aspect of the concept to evaluate in the context of their treatment. The sponsor provided sufficient evidence of content validity for the electronic Psoriasis Symptom Diary to support the labeling claims related to itching, pain, and scaling as proposed.

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

Descriptive statistics: At baseline, patients' responses were generally higher than the midpoint on the 11-point scale, indicating that patients were experiencing moderate to severe skin-related symptoms in both the phase 2 and phase 3 trials as shown in the table below (taken from page 59/1528):

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Table 12. Descriptive Statistics of Key Psoriasis Symptom Diary Severity Items at Baseline

Psoriasis Symptom Diary Severity Item	n	Mean (SD)	Percentile			Range
			25th	50th	75th	
Phase 2						
Itching	169	6.4 (2.5)	4.6	7.0	8.4	0-10
Pain	169	4.7 (3.0)	2.4	4.8	7.2	0-10
Scaling	169	6.6 (2.3)	5.1	7.0	8.4	0-10
Phase 3						
Itching	820	6.3 (2.4)	4.5	6.6	8.1	0-10
Pain	820	5.3 (3.0)	2.8	5.5	7.7	0-10
Scaling	820	6.3 (2.5)	4.6	6.7	8.3	0-10

Test-retest reliability: Test-retest reliability based on intra-class correlation coefficients (ICCs) was computed for **itching, pain, and scaling** using data from screening week 1 as the “test” administration and data from screening week 2 as the “retest” administration. The table below (from page 60/1528 of the dossier) shows the ICC for itching, pain, and scaling were at least 0.90:

Table 13. Test-Retest Reliability of Itching, Pain, and Scaling Severity Items: Intraclass Correlation Coefficient

Psoriasis Symptom Diary Severity Item	Intraclass Correlation Coefficient (95% CI)	
	Phase 2 (N = 128)	Phase 3 (N = 147)
Itching	0.91 (0.88, 0.94)	0.93 (0.90, 0.95)
Pain	0.93 (0.90, 0.95)	0.91 (0.87, 0.93)
Scaling	0.90 (0.87, 0.93)	0.91 (0.88, 0.94)

Construct Validity: Construct validity describes the relationships among multiple indicators of a construct and the degree to which they follow predictable patterns. The sponsor evaluated construct validity for **itching, pain, and scaling** items through targeted correlation analyses; the magnitude and direction of the resulting correlation coefficients were compared with respect to specific hypotheses and also to Cohen's (1988) guideline for interpreting correlation coefficients i.e., absolute values of correlations of 0.50 or greater are considered strong, correlations that fall between 0.10 and 0.50 are moderate, and those less than 0.10 are small or weak.

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The Table 14 and 15 below (from page 62 & 63/1528 of the dossier) shows that the correlations between the **itching, pain, and scaling** items and three additional severity items (stinging, burning, pain/cracking) were strong ($r > 0.50$) in the phase 2 and phase 3 trials. The range of correlations for itching, pain, and scaling is between 0.59 and 0.78 in phase 2 and between 0.69 and 0.74 in phase 3, indicating a set of items that is strongly related:

Table 14. Inter-Item Validity Correlations at Baseline Between Key Psoriasis Symptom Diary Severity Items

Psoriasis Symptom Diary Severity Item	Itching	Pain	Scaling	Stinging	Burning
Phase 2 (N = 169)					
Itching	—				
Pain	0.63	—			
Scaling	0.78	0.59	—		
Stinging	0.67	0.85	0.54	—	
Burning	0.64	0.87	0.51	0.97	—
Pain/cracking	0.68	0.89	0.68	0.80	0.81
Phase 3 (N = 820)					
Itching	—				
Pain	0.74	—			
Scaling	0.77	0.69	—		
Stinging	0.76	0.89	0.69	—	
Burning	0.75	0.87	0.67	0.91	—
Pain/cracking	0.75	0.92	0.75	0.87	0.85

Note: all correlations are significantly different from zero, $P < 0.01$.

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Table 15. Validity Correlations Between Itching, Pain, and Scaling Severity Items With PASI, IGA, DLQI, EQ-5D

Psoriasis Symptom Diary Severity Item	PASI		IGA ^a		DLQI		EQ-5D
	Baseline	Week 12	Baseline	Week 12	Total	Item 1	
Phase 2 (N = 148 to 169)							
Itching	0.06	0.57*	-0.00	0.58*	0.49*	0.69*	-0.04
Pain	0.001	0.39*	0.05	0.41*	0.60*	0.55*	-0.17
Scaling	-0.01	0.49*	-0.01	0.57*	0.43*	0.50*	0.08
Phase 3 (N = 721 to 820)							
Itching	0.15*	0.63*	0.24*	0.68*	0.57*	0.72*	-0.23*
Pain	0.17*	0.59*	0.29*	0.59*	0.56*	0.65*	-0.26*
Scaling	0.13*	0.68*	0.22*	0.73*	0.54*	0.56*	-0.17*

* $P < 0.01$.

DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index.

^a IGA in phase 2 and phase 3 were different versions. IGA in phase 3, referred to as IGA mod 2011, did not include category 5 (deep dark red coloration; very severe thickening with hard edges; and very severe/very coarse scaling covering all lesions).

Ability to Detect Change:

The sponsor evaluated the ability of **itching, pain, and scaling** to detect change using the following methods:

1. The correlations between changes in itching, pain, and scaling scores and changes in the PASI, IGA, and DLQI from baseline to week 12 were evaluated.
2. The effect sizes of the mean change in itching, pain, and scaling scores were computed.
3. The mean change in itching, pain, and scaling scores by responder and non-responder groups based on the PASI were evaluated.

The results are shown in the Tables 18, 19, & 20 below taken from pages 66, 67 & 68/1528 of the Evidence Dossier:

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Table 18. Responsiveness of Itching, Pain, and Scaling Severity Items: Correlations Using Change From Baseline To Week 12 for the PASI, IGA, and DLQI

Psoriasis Symptom Diary Item change (BL to week 12)	PASI Change (BL to Week 12)	IGA ^a Change (BL to Week 12)	DLQI (BL to Week 12)
Phase 2 (N = 138 - 147)			
Itching	0.61	0.58	0.57
Pain	0.37	0.41	0.54
Scaling	0.59	0.60	0.57
Phase 3 (N = 666 – 682)			
Itching	0.56	0.62	0.66
Pain	0.50	0.53	0.63
Scaling	0.55	0.62	0.65

All correlations are significant at $P \leq 0.01$.

BL = baseline; DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; PASI = Psoriasis Area and Severity Index.

^a IGA in phase 2 and phase 3 were different versions. IGA in phase 3, referred to as IGA mod 2011, did not include category 5 (deep dark red coloration; very severe thickening with hard edges; and very severe/very coarse scaling covering all lesions).

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Table 19. Responsiveness of Itching, Pain, and Scaling Severity Items: Mean Change (Baseline – Week 12) Effect Size

Psoriasis Symptom Diary Item	Change (BL – Week 12) mean (SD)	Effect Size^a
Phase 2 (N = 148)		
Itching	-2.7 (3.0)	1.1
Pain	-2.1 (2.6)	0.7
Scaling	-2.8 (3.1)	1.2
Phase 3 (N = 708)		
Itching	-3.6 (3.2)	1.5
Pain	-3.0 (3.3)	1.0
Scaling	-3.5 (3.3)	1.4

BL = baseline; SD = standard deviation.

^a The absolute value of the effect size is presented.

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Table 20. Responsiveness: Mean Change From Baseline to Week 12, by PASI Response Groups

Psoriasis Symptom Diary item	PASI Response Mean (SD) n		
	PASI 75 Responder	Partial Responder	Nonresponder
Phase 2	(N = 43)	(N = 31)	(N = 73)
Itching	-5.1 (2.7) 43	-3.2 (2.5) 31	-1.1 (2.3) 73
Pain	-3.4 (2.6) 43	-2.6 (2.65) 31	-1.1 (2.2) 73
Scaling	-5.5 (2.6) 43	-3.5 (2.6) 31	-0.9 (2.1) 73
Phase 3	(N = 387)	(N = 105)	(N = 259)
Itching	-5.3 (2.6) 364	-3.5 (2.4) 98	-1.0 (2.7) 246
Pain	-4.4 (3.0) 364	-3.1 (2.6) 98	-0.9 (2.8) 246
Scaling	-5.2 (2.7) 364	-3.7 (2.4) 98	-0.8 (2.7) 246

PASI = Psoriasis Area and Severity Index.

PASI 75 responder is a subject who achieved a $\geq 75\%$ improvement from baseline in PASI score; a partial responder is a subject who achieved a $\geq 50\%$ improvement from baseline but $< 75\%$; a nonresponder is a subject who achieved a $< 50\%$ improvement from baseline.

6 INTERPRETATION OF SCORES

To interpret meaningful change, the sponsor used anchor-based methods. Anchor-based methods use an external criterion to categorize patients into groups each reflecting an a priori determined change grouping (e.g., no change, large positive change, large negative change).

Using an anchor-based method in the phase 2 trial, Psoriasis Symptom Diary scores (means and standard deviations [SDs]) were computed for each level of change reported by patients in response to a Patient Global Impression of Change (PGIC) item at the week-12 assessment. PGIC administered at treatment week 12: Since the start of this study, how would you rate the overall impact of psoriasis on your life right now?

- A great deal worse
- Moderately worse
- A little worse
- About the same

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- A little better
- Moderately better
- A great deal better

The sponsor stated that in this way, the responder criterion is set to include patients who report the overall impact of their psoriasis to be a little better, moderately better, and a great deal better. Table 21 below taken from page 70/1528 of the Evidence Dossier describes the Psoriasis Symptom Diary item change scores from baseline to week 12 in the phase 2 trial in terms of how the patients evaluated the overall impact of psoriasis on their life since starting treatment.

Table 21. Psoriasis Symptom Diary Item Change Scores by PGIC (Week 12 - Baseline)

Change		PGIC: Since the start of this study, how would you rate the overall impact of psoriasis on your life right now [at Week 12]? ^a					Total
		Moderately Great Deal Worse	Little Worse	About the Same	Little Better	Moderately Great Deal Better	
1: Severity-itching	Mean ^b	.40	-.23	-1.30	-2.18 ^c	-4.6	-2.69
	N	14	12	24	27	61	138
	SD	2.44	3.10	1.68	1.91	2.52	2.98
9: Severity-pain	Mean ^b	.11	-.47	-.97	-2.20 ^c	-3.30	-2.09
	N	14	12	24	27	61	138
	SD	2.93	1.38	1.78	1.82	2.61	2.59
11: Severity-scaling	Mean ^b	.17	-.40	-.85	-2.32 ^c	-4.91	-2.79
	N	14	12	24	27	61	138
	SD	2.08	2.44	1.53	2.19	2.75	3.09807

PGIC = Patient Global Impression of Change.

^a Mean comparisons between PGIC levels was tested using via one-way ANOVA.

^b Significant at the 0.001 level.

^c Responder criterion or the point at which a change in item score reflects a clinically meaningful and interpretable change in the concept assessed.

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Reviewer's comment: While use of global ratings of change is acceptable as an exploratory measure to be used as an anchor, there are limitations of global questions that should be considered. These include (a) the global is often too general to be used as an anchor; (b) as single-item question of complex concepts, global questions have inherent concerns with content validity; and (c) global items assessing change often require patients to recall over lengthy periods of time and make a comparison to their baseline status, which is difficult for patients to do. In addition to anchor-based methods, the PRO Guidance recommends cumulative distribution function curves as an aid for interpretation of study results based on a well-developed outcome assessment.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

The following translation certificates for the Psoriasis Symptom Diary were provided: Hungarian, Icelandic, Italian, Korean, Portuguese, Polish, Malay, Romanian, Russian, Chinese, Spanish, Swedish, Turkish, Danish, Dutch, Finnish, French, and German.

8 REVIEW USER MANUAL

The sponsor has provided the full instructions for use of the proposed Psoriasis Symptom Diary. A user manual as such was not provided.

9 PROTOCOL AND ANALYSIS PLAN

Secukinumab Phase 3 clinical trials: The following randomized, double-blind, placebo controlled, and multicenter phase 3 clinical trials were conducted:

1. Study CAIN457A2302
2. Study CAIN457A2303

Please refer to the clinical and statistical reviews for additional information on protocol design and endpoint analysis.

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

/s/

YASMIN A CHOUDHRY
09/08/2014

ELEKTRA J PAPADOPOULOS
09/08/2014

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: August 27, 2014

Requesting Office or Division: Division of Dermatology and Dental Products

Application Type and Number: BLA 125504

Product Name and Strength: Cosentyx (Secukinumab) For Injection, 150 mg/vial
Cosentyx (Secukinumab) Injection, 150 mg/mL Prefilled Syringe
Cosentyx (Secukinumab) Injection, 150 mg/mL SensoReady Pen

Product Type: Single ingredient product and Drug-device combination product

Rx or OTC: Rx

Applicant/Sponsor Name: Novartis

Submission Date: October 14, 2013

OSE RCM #: 2013-2700

DMEPA Primary Reviewer: Carlos M Mena-Grillasca, RPh

DMEPA Team Leader Kendra Worthy, PharmD

DMEPA Associate Director: Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

As part of the evaluation for the new BLA 125504, DDDP requested DMEPA evaluate the proposed container labels, carton labeling, and Full Prescribing Information for Cosentyx for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	n/a
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	n/a
Other	n/a
Labels and Labeling	D

n/a=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market Cosentyx in 150 mg/vial, and 150 mg/mL prefilled syringes, and SensoReady Pen autoinjectors. The proposed dose is 300 mg given as 2 x 150 mg subcutaneous injections. However, the approved dose might not be determined until after the Advisory Committee meeting and may include a 150 mg dose. The Sponsor submitted carton labeling for single packs of each dosage form (vial, prefilled syringe, SensoReady Pen) and packs of 2 units (2 prefilled syringes or 2 SensoReady Pens). Therefore, we find the proposed packaging configurations adequate for either a 150 mg or 300 mg dose.

We note that the applicant performed Human Factor studies for the SensoReady Pen and the prefilled syringe (PFS). However, DMEPA did not request that the applicant perform a HF study for the PFS as it is considered a ‘standard’ prefilled syringe.¹

The applicant followed an iterative process during the design of the autoinjector in which they revised the Instructions for Use (IFU) to address the user errors observed during the Human Factor studies. However, some failure modes observed were not mitigated with the revisions made to the Instructions for Use. These residual risks include: (1) failure to activate the autoinjector, (2) failure to hold the autoinjector until the second click, and (3) failure to identify the correct end of the pen to perform the injection. DMEPA considers these residual risks no different than those that occur with other auto injectors currently marketed and of minimal risk to the patient’s safety.

We note that the container labels, (b) (4) and carton labeling do not include the dosage form statement (e.g. for injection or injection). Although all the labels and labeling indicate that the product is for “Single Use Only”, they do not include the statement “Discard Unused Portion”. We note that the descriptive statement “Single Use Prefilled” precedes both the “SensoReady Pen” and “Syringe” dosage forms statements (i.e. “Single Use Prefilled SensoReady Pen” and “Single Use Prefilled Syringe”). This becomes repetitive and makes the dosage forms statements looks similar, which may lead to selection errors.

The strength statement for the vial formulation is presented as (b) (4) mg per vial due to an overfill required to deliver a 150 mg dose. Per the Draft Guidance to Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, the amount of overfill should not be declared on the labels.² Therefore, the strength statement for the vial formulation should be declared as 150 mg/vial. Finally, we note the use of trailing zeros on the reconstitution and list of ingredients statements.

We provide recommendations to address these container labels and carton labeling issues in section 4.2.

In addition, we reviewed the Full Prescribing Information, Medication Guide, and Instructions for use. We found areas for improvement and provided comments during the labeling meeting (See Appendix H).

¹ Mena-Grillasca M. Human Factors Memo for Cosantix (IND 100418). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2013 FEB 05. OSE RCM No.: 2012-2874.

² <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389069.pdf>

4 CONCLUSION & RECOMMENDATIONS

We find the proposed packaging configurations in single packs and two packs adequate for the 150 mg and 300 mg doses. However, DMEPA recommends the following be implemented prior to approval of this application.

4.1 RECOMMENDATIONS FOR THE REVIEW DIVISION

We provide recommendations to the FPI for consideration by the review division. See tracked changes in Appendix H.

4.2 RECOMMENDATIONS FOR NOVARTIS

A. General Comments for all Container Labels and Carton Labeling

1. Add the dosage form statement to appear under the proper name, as follows.
The SensoReady Pen and prefilled syringe labels and labeling:

Cosentyx
(secukinumab)
Injection

The vial label and labeling:

Cosentyx
(secukinumab)
For Injection

2. Relocate the  graphic away from the proprietary name. As currently presented the graphic is in close proximity to the proprietary name and can be misinterpreted as part of the proprietary name.

B. SensoReady Pen Carton Labeling, 2 x 150 mg/mL (Trade and Sample)

1. Revise the strength statement to read:
150 mg/mL
2 SensoReady Pens

C. SensoReady Pen Carton Labeling, 150 mg/mL (Trade and Sample)

1. Revise the strength statement to read:
150 mg/mL
1 SensoReady Pen

D. SensoReady Pen Container Label, 150 mg/mL (Trade and Sample)

1. Revise the strength statement to read:
150 mg/mL
SensoReady Pen

E. Pre-filled Syringe Outer Carton Labeling, 2 x 150 mg/mL (Trade and Sample)

1. Revise the strength statement to read:
150 mg/mL
2 Prefilled Syringes

F. Pre-filled Syringe (b) (4) Inner (b) (4) Labeling, 2 x 150 mg/mL (Trade and Sample)

1. Revise the strength statement to read:
150 mg/mL
2 Prefilled Syringes

G. Prefilled Syringe Outer Carton Labeling, 150 mg/mL (Trade and Sample)

1. Revise the strength statement on the PDP to read:
150 mg/mL
1 Prefilled Syringe

H. Prefilled Syringe (b) (4) Inner (b) (4) Labeling, 150 mg/mL (Trade and Sample)

1. Revise the strength statement to read:
150 mg/mL
1 Prefilled Syringe
2. Relocate the information that appears below and to the right of the Rx only statement to the bottom panel to make room for the required information on the PDP (proprietary and proper names, strength, NDC, warning statements).

I. Prefilled Syringe Container Label, 150 mg/mL

1. Delete the storage and handling statements to improve readability of the label. The storage information is not required on small labels per 21 CFR 610.60(c).
2. Revise the statement "Single Use" to read "Single Use Only".

J. Vial Carton Labeling

1. Revise the strength statement from “ (b) (4) ” to “150 mg/vial”. Per *Draft Guidance to Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products*¹, the amount of overfill should not be declared on the labels.
2. Revise the statement “Single Use Vial” on the PDP to read “Single Use Vial, Discard Unused Portion” and relocate to appear below the statement “For Subcutaneous Use Only”.
3. Revise the diluent statement that reads “Sterile Water for Injection” to read “Sterile Water for Injection, USP” on the PDP and back panel.
4. Revise the statement that reads “* (b) (4) ” to read “Reconstitute with 1 mL of Sterile Water for Injection, USP to obtain a concentration of 150 mg/mL of secukinumab”. Then relocate the list of ingredients to the back panel to read “After reconstitution each mL contains....”.
5. Delete the trailing zeroes from the reconstitution statement from “1.0 mL of Sterile Water for Injection” and “0.60 mg/mL polysorbate 80” to read “1 mL of Sterile Water for Injection, USP” and “0.6 mg/mL polysorbate 80”.
6. Revise the statement “ (b) (4) ” to read “See package insert for dosage, reconstitution, and administration information.”
7. Consider revising the back panel to remove excessive use of bold type font. Use of bold font should be reserved to highlight important information.

K. Vial Container Label

1. Revise the strength statement from “ (b) (4) *” to read “150 mg/vial”. Per *Draft Guidance to Industry: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products*¹ the amount of overfill should not be declared on the labels.
2. Delete the statement “*The reconstituted solution contains 150 mg/mL” to unclutter and improve readability of the label. After implementation of comment K.1., this statement is no longer needed.

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389069.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cosentyx that Novartis submitted on October 14, 2013.

Table 2. Relevant Product Information for Cosentyx	
Initial Approval Date	n/a
Active Ingredient	Secukinumab
Indication	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Route of Administration	Subcutaneous
Dosage Form	Powder for Injection (vial) Solution for Injection (pre-filled syringe and auto-injector)
Strength	150 mg per vial 150 mg/mL (pre-filled syringe and auto-injector)
Dose and Frequency	300 mg by subcutaneous injection with initial dosing at weeks 0, 1, 2, and 3 followed by monthly maintenance dosing starting at week 4. Each 300 mg dose is given as 2 subcutaneous injections of 150 mg
How Supplied	150 mg powder for injection in Single Use vials 150 mg/mL injection in a single dose pre-filled syringe 150 mg/mL injection in a single dose autoinjector In cartons of 1 unit or 2 units
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F)
Container Closure	n/a

APPENDIX C. PREVIOUS DMEPA REVIEWS

B.1 Methods

We searched the L: drive on June 23, 2014 using the terms, Cosentyx and Secukinumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified one previous relevant review¹, and we confirmed that our previous recommendations to the Human Factors protocol were considered.

¹ Mena-Grillasca C. Label and Labeling Review for Secukinumab (IND 100418). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 May 11. 9 p. OSE RCM No.: 2012-445.

APPENDIX D. HUMAN FACTORS STUDY

C.1 Study Design

Prefilled Syringe

A validation study was carried out with participants representative of potential users. 105 participants received a realistic, pre-defined training, returning for a simulated session either one week or one month after their training; 33 participants were untrained and carried out the simulated use assessment without support, representing the worst case scenario.

SensoReady Pen

Development of the SensoReady Pen included a risk analysis to identify potential hazards, the harm to the user and the severity of the harm, as well as other design control activities that provided the configurations evaluated in formative study and validation testing. The formative studies were conducted to derive information from user interaction with devices and included the evaluation of competitors and potential partner devices and observational simulated use studies to assess use and comprehension of the IFU.

Validation studies were carried out with 165 participants representative of potential users. Ninety-four of these participants received realistic, predefined training and returned for a simulated use assessment session either one week or four weeks after their training. Seventy-one participants were untrained and carried out their simulated use assessment without support, representing the worst case use scenario.

C.2 Results

Prefilled Syringe

The study results showed that 104/105 trained participants, and 33/33 untrained participants delivered their first injection successfully. The results also showed that 18/138 participants experienced some confusion while performing their injections.

- Injection technique intentionally not as instructed leading to slight reduction in dose (e.g. checking that the medication flows/the needle is not blocked by pressing a few drops out before injection)
- Injection technique unintentionally not as instructed leading to slight reduction in dose (e.g. inadvertently pushing plunger slightly before needle inserted into skin)
- Close call (e.g. pulling on the plunger when removing the needle cap but recovering before the plunger was removed)
- Confusion regarding device operation (e.g. thinking that the needle had been left in the skin after the needle guard was deployed)
- Inability to comprehend instruction that has associated high severity harm (e.g. the meaning of a “sharps container”)

- Inadvertent removal of the plunger (including the rubber stopper) completely out of the syringe barrel

The Instructions for Use was modified to address the reported confusions above.

SensoReady Pen

The study results found that during the first unsupervised injection:

- Seven (7/94) trained participants did not complete the injection successfully due to failure to activate the SensoReady Pen, to hold the SensoReady Pen against the injection site until the 2nd 'click' (5 instances), and due to moderator intervention (two instances) to prevent possible needle stick injuries (identifying the correct end of the pen to perform injection)
- Six (6/71) untrained participants failed to deliver their first unsupervised injection due to failure to failed to hold the SensoReady Pen against the injection site until the 2nd 'click' During the one week and four week assessments, two (2/56) and five (5/38) trained participants failed to perform the injection respectively due to failure to hold the SensoReady Pen against the injection site until the 2nd 'click.' These results were intended to demonstrate user performance after some time has elapsed between receiving training and performing the next injection.

In addition, there were 20/165 participants (trained and untrained) experienced difficulty but were able to successfully complete an injection. These difficulties were due to:

- Green Plunger Confusion: Confusion over the appearance or the motion (e.g. direction or speed) of the SensoReady Pen's green plunger.
- Confusion over how to activate the injection: tried to activate the SensoReady Pen by pressing a button rather than pushing down on the device body to trigger the injection (1st 'click').
- Inadvertent 2nd 'click' removal: when the mechanism activated on the 2nd 'click', the injector 'sprang-up' out of the participant's hand as they applied insufficient grip and downward force to the injector to keep it in place. Participants therefore received a 'clinically effective' albeit 'wet' injection
- Struggle to maintain downward pressure: struggled to keep the SensoReady Pen pressed firmly against the skin until the 2nd 'click' was heard and the green plunger had stopped moving.

Several modifications to the Instructions for Use have been made to address the task failures associated with the 2nd click issue.

APPENDIX G. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Cosentyx labels and labeling submitted by Novartis on October 14, 2013.

- Container labels
- Carton labeling
- Professional Sample Container Labels and Carton Labeling
- Instructions for Use (no image)
- Medication Guide (no image)
- Full Prescribing Information (no image)

D.2 Label and Labeling Images



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

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

CARLOS M MENA-GRILLASCA
08/28/2014

KENDRA C WORTHY
08/28/2014

LUBNA A MERCHANT
08/28/2014

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 15, 2014

TO: Mathew White , Regulatory Project Manager
Amy Weitach, M.D., Medical Officer
David Kettl , M.D., Medical Team Leader
Division of Dermatologic and Dental Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125504

APPLICANT: Novartis Pharmaceuticals Corporation

DRUG: Cosentyx (secukinumab)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of plaque-type psoriasis (b) (4)

CONSULTATION REQUEST DATE: December 27, 2013
 CLINICAL INSPECTION SUMMARY DATE: August 22, 2014
 DIVISION ACTION GOAL DATE: October 10, 2014
 PDUFA DATE: October 24, 2014

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Cosentyx for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

The pivotal study CAIN457A2302, entitled “A randomized, double-blind, placebo controlled, multicenter study of subcutaneous secukinumab to demonstrate efficacy after twelve weeks of treatment, and to assess the safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis Efficacy of Response And Safety of 2 Fixed Secukinumab Regimens in Psoriasis (ERASURE)”, and the pivotal study CAIN457A2303, entitled “A randomized, double-blind, double-dummy, placebo controlled, multicenter study of subcutaneous secukinumab to demonstrate efficacy after twelve weeks of treatment, compared to placebo and etanercept, and to assess the safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis Full year Investigative eXamination of secukinumab vs. eTanercept Using 2 dosing Regimens to determine Efficacy in psoriasis (FIXTURE)” were inspected in support of the indication.

The clinical site of Drs. Papp and Szepietowski were selected for inspection because they were among the larger enrolling sites and study treatment exhibited somewhat greater efficacy than most other sites.

The clinical site of Dr. Bardur Sigurgeirsson was selected and inspected independently by the European Medicines Agency (EMA). The findings of the inspection presented in this document are based on the Integrated Inspection Report shared by the EMA with FDA.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Dr. Kim Papp Probity Medical Research Waterloo, ON. N2J 1C4, Canada	CAIN457A2302/ 1023/ 24	5-15 May, 2014	NAI
Dr. Kim Papp Probity Medical Research Waterloo, ON. N2J 1C4, Canada	CAIN457A2303/ 2128/ 10	5-15 May, 2014	NAI
Prof. Dr. Jacek Szepietowski Samodzielny Publiczny Szpital Kliniczny nr 1 Wroclaw 50-368 Poland	CAIN457A2303/ 3420/ 55	28 Apr–8 May, 2014	NAI
Dr. Bardur Sigurgeirsson Cutis Kopavogur IS-201 Iceland	CAIN457A2303/ 3200/ 51	11-14 Mar 2014	NA

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

NA = Conducted by EMA; OSI classifications Not Applicable.

1. Dr. Kim Papp

Probity Medical Research
Waterloo, ON. N2J 1C4
Canada

- a. **What was inspected:** At this site, for Protocol CAIN457A2302, 32 subjects were screened, eight subjects failed screening, and 24 subjects were enrolled and completed the study through the follow up visit of Week 52. For Protocol CAIN457A2303, 17 subjects were screened, six subjects failed screening, one subject transferred, seven subjects completed the study, and three subjects were withdrawn from the study. For both studies, records reviewed included financial disclosure forms, source data, case report forms (CRFs), laboratory certifications, test article accountability, and correspondence of the site with the sponsor and IRB. Informed consent forms were reviewed for all subjects of both studies. In addition, the source data for eligibility criteria and adverse event reporting for all subjects in both studies was compared with the data listings and no discrepancies were observed.
- b. **General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Prof. Dr. Jacek Szepietowski

Samodzielny Publiczny Szpital
Kliniczny nr 1
Wroclaw 50-368
Poland

- a. **What was inspected:** At this site for Protocol CAIN457A2303, 55 subjects were enrolled, and all 55 enrolled subjects completed the induction portion study (through Visit 8), with two subjects not completing the maintenance portion of the protocol. The records of 34 enrolled subjects were reviewed. Source records were compared with data listings and no discrepancies were noted. Records reviewed included IRB, sponsor and monitor communications, delegation of authority, and computerized data collection. Other records reviewed included informed consent, inclusion/exclusion criteria, adverse events, concomitant medications, test article accountability and storage, and personnel training.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Dr. Bardur Sigurgeirsson
Cutis
Kopavogur IS-201
Iceland

This clinical investigator inspection was conducted by EMA and the results communicated to OSI. The major structure of EMA inspections consists of classification of regulatory deficiencies as Critical (CR), Major (MA), and Minor. Given below are definitions and potential consequences of these classifications:

- **Critical:** Conditions, practices or processes that adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of the data. Possible consequences include rejection of data and/or legal action required.
- **Major:** Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Possible consequences include data being rejected and/or legal action required.
- **Minor:** Conditions, practices or processes that would not be expected to adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of the data. Possible consequences include the need for improvement of conditions, practices and processes.

The purpose of the inspection was to evaluate compliance with EMA-applicable regulations and GCP, and verify, in particular, where such compliance, or lack thereof, had an impact on the validity of the data or the ethical conduct of the study.

- a. What was inspected:** This inspection of Protocol CAIN457A2303 was conducted as a data audit for EMA (EMA Inspection Reference: INS/GCP/2013/031). For this study, 54 subjects were screened and 51 subjects were randomized to the study. The inspection included a review of the investigator's experience with clinical trials, ongoing clinical trials, organizational makeup, laboratory resources, investigator site files (paper), subject medical records (electronic), source documentation, delegation of authority, training documentation, communications with the ethics committee, monitoring correspondence, adverse events, laboratory certifications, and test article accountability and storage. Informed consent forms were reviewed for all subjects. All line listing data was compared with source data for Subjects 001, 015, 020, and 033.

- b. General observations/commentary:** All consent forms were signed by the subjects, an investigator, and a study nurse. In some cases the most updated version of the consent form was not provided to the subject at the earliest possible visit. Prior to the conduct of this study (A2303), a related study (A2302) was also conducted. To address any question of bias regarding subject selection and study assignment, Dr. Sigurgeirsson drafted a memo stating that Novartis provided no direction on how to select study subjects, that the site was aware that no external factors should influence how subjects were to be assigned to either study, that subjects were not allowed to select which study they would be assigned to, and that recruitment to Study A2302 predated recruitment to Study A2303 by a brief period of time. Dr. Sigurgeirsson said that subjects were randomly assigned to either study. At a later date, Novartis increased the recruitment for Study A2303.

The comparison of source data with line listings revealed isolated protocol violations and data discrepancies for the records of the four subjects reviewed. These did not have an impact on primary efficacy assessment or human subject safety. An SAE for Subject 007 (surgical removal of an atheroma on February 8, 2012) was reported late (May 22, 2012).

c. Assessment of data integrity:

The EMA summarized the inspection noting that there were no critical findings, five major findings and nine minor findings. The findings ranged from isolated data discrepancies to delayed reporting of an SAE to minor documentation issues. The EMA concluded that despite the findings, the data at this site were reliable and suitable for assessment.

Having reviewed EMA's inspection report on the conduct of Protocol CAIN457A2303 at Dr. Sigurgeirsson's site, OSI is in agreement that the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

FDA inspected Dr. Papp's and Dr. Szepietowski's clinical investigator sites. Neither Dr. Papp nor Dr. Szepietowski was issued a Form FDA 483. The final classification of these inspections was No Action Indicated (NAI).

EMA inspected Dr. Sigurgeirsson's clinical investigator site. No critical findings were noted. The major and minor findings noted by EMA appeared to be isolated examples and unlikely to adversely affect safety or efficacy assessments. The data generated by these three clinical sites appear adequate in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
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/s/

ROY A BLAY
08/15/2014

JANICE K POHLMAN
08/15/2014

KASSA AYALEW
08/15/2014



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: May 19, 2014
From: Keith Marin, Combination Products Team Leader, WO66, RM 2567
General Hospital Devices Branch, DAGID, ODE, CDRH
To: Matthew White, Regulatory Health Project Manager,
OMPT/CDER/OND/ODEIII/DDDP
Subject: CDRH Consult, CTS ICC 1300617/S002, BLA 125504, PFS and AI to
deliver COSENTYX™ (secukinumab)
Consults: Jason To, Biomedical Engineer, CDRH/ODE/DAGRID/GHDB

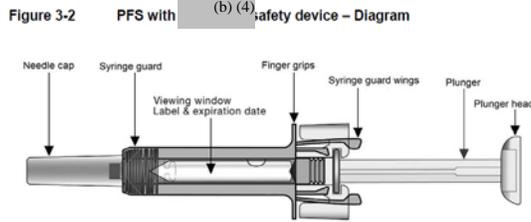
1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding BLA 125504. The device constituent of this combination product consists of a PFS and AI to deliver COSENTYX™ (secukinumab). This consult consists of a comprehensive BLA and device labeling review.

2. Device Descriptions

The primary container closure for the drug product is the (b) (4) 1.0 mL pre-filled syringe with 27G X 1/2 inch staked needle with (b) (4) plunger stopper. A rubber needle shield encapsulates the needle; the rigid shell stabilizes and protects the closure. The syringe barrel, needle and plunger stopper are (b) (4).

For the PFS product presentation, the container closure system also includes the (b) (4) as a safety mechanism to reduce occurrence of accidental needle sticks. The (b) (4) does not contact the drug product. The device was cleared by FDA under 510(k) premarket submission (b) (4).



The (b) (4) auto-injector is a fixed single dose, disposable, (b) (4) drug delivery device developed by (b) (4) is designed to provide a convenient means to inject a single medication subcutaneously from a prefilled syringe. The device consists of Front Subassembly and Rear Subassembly that are designed to enclose drug product contained in (b) (4) 1.0 mL pre-filled syringe with 27G X 1/2 inch stake-on needle. The syringe holds the entire dose, which can be expelled as a fixed dose. The labeled volume is 1.00ml, and the accuracy for the minimum dose is accordance to the pen-injector standard. The needle is hidden during the entire injection process

The (b) (4) consists of (b) (4) sub-assemblies specifically designed to enclose a pre-filled in a (b) (4) 1.0 mL syringe with 27GX 1/2 inch stake-on needle. While the injection is taking place, the user can hear two audible clicks: start and finish of the dose. After the injection, the Shield is automatically locked to prevent needle stick.

The AI is made up of the following parts/features (as shown in Figure 3-1):

- Cap (protects the needle before use)
- Cap Seal (tamper evidence feature)
- RNS (protects needle before use) – part of the PFS
- Needle (inserts into the skin) – part of PFS
- Needle Guard (Sharps Injury Prevention Feature - SIPF)
- Inspection Window (allows user to check the progress of the injection (green indicator) and check the appearance of the drug before use)
- Green Indicator (shows the progress of the injection as it slowly progresses through the inspection window during injection)

3. Documents Reviewed

BLA 125504

MAF (b) (4)

(b) (4)

DMF (b) (4)

(b) (4)

4. CDRH Review and Comments

DMF (b) (4)

(b) (4) 1.0 mL pre-filled syringe with 27G X 1/2 inch stake-on needle was reviewed in September 2013 and appears to be adequate.

(b) (4) is included with the PFS presentation as a safety mechanism to reduce occurrence of accidental needle sticks. The device was cleared by FDA under 510(k) premarket submission (b) (4)

MAF (b) (4) Injector

Biocompatibility

The recommended biocompatibility testing for the (b) (4), based upon its use in the combination product, is identified in ISO 10993-1 "Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing". These tests include Cytotoxicity, Sensitization, and Irritation or Intracutaneous Reactivity for the biological effects of a device that is categorized as a surface device having limited contact duration (<24 h) with human skin. The plastic components of (b) (4) that have direct contact with the user skin were tested by (b) (4) in the US and the test reports are included in Attachment 6.

Test: Cytotoxicity

Protocol: page 8-15, MAF (b) (4)

Acceptance criteria:

BLA 125504, ICC1300617/S002
 Cosentyx
 Prefilled Syringe and Autoinjector to deliver Cosentyx

Table 1: Qualitative morphological grading of cytotoxicity of extracts

Grade	Reactivity	Conditions of all Cultures
0	None	Discrete intracytoplasmic granules, no cell lysis, no reduction of cell growth.
1	Slight	Not more than 20% of the cells are round, loosely attached and without intracytoplasmic granules, or show changes in morphology; occasional lysed cells are present; only slight growth inhibition observable.
2	Mild	Not more than 50% of the cells are round, devoid of intracytoplasmic granules, no extensive cell lysis; not more than 50% growth inhibition observable.
3	Moderate	Not more than 70% of the cell layers contain rounded cells or are lysed; cell layers not completely destroyed, but more than 50% growth inhibition observable.
4	Severe	Nearly complete or complete destruction of the cell layers.

Results:

Table 5: Test Results

	Reactivity 24 hrs	Grade 24 hrs	Reactivity 48 hrs	Grade 48 hrs
Test Article #1	None	0	None	0
Test Article #2	None	0	None	0
Test Article #3	None	0	None	0
Controls				
Positive #1	Moderate	3	Severe	4
Positive #2	Moderate	3	Severe	4
Positive #3	Moderate	3	Severe	4
Negative #1	None	0	None	0
Negative #2	None	0	None	0
Negative #3	None	0	None	0
Reagent #1	None	0	None	0
Reagent #2	None	0	None	0
Reagent #3	None	0	None	0

ISO Scoring Key: 0 = None (No reactivity), 1 = Slight Reactivity, 2 = Mild Reactivity, 3 = Moderate Reactivity, 4 = Severe Reactivity

Conclusion: no reactivity from test subjects

Test: Sensitization

Protocol: page 8-15, MAF (b) (4)

Acceptance criteria:

Table 1: Magnusson and Kilgman Scale

Grading Scale	Patch Test Reaction
0	No visible change
1	Discrete or patchy erythema
2	Moderate and confluent erythema
3	Intense erythema and/or swelling

Adopted from ISO 10993-10:2010 Biological Evaluation of Medical Devices – Part 10: Test for Irritation and Skin Sensitization

Results:

Table 7: Skin Reaction Scores and Animal Weights (SCI Extraction)

Animal Number	Sex	24 Hour Score		48 Hour Score		Weight (g)	
		Test	Control	Test	Control	Pre-Test	Post-Test
10293	M	0	0	0	0	490	610
10294	M	0	0	0	0	474	544
10295	M	0	0	0	0	461	558
10296	M	0	0	0	0	468	550
10297	M	0	0	0	0	483	562
10298	M	0	0	0	0	464	578
10338	F	0	0	0	0	330	498
10339	F	0	0	0	0	320	410
10340	F	0	0	0	0	310	412
10341	F	0	0	0	0	312	420
10342	F	0	0	0	0	327	421
10343	F	0	0	0	0	309	410
Negative Control Group							
10299	M	0	0	0	0	463	632
10300	M	0	0	0	0	421	547
10301	M	0	0	0	0	356	469
10344	F	0	0	0	0	323	465
10345	F	0	0	0	0	311	410
10346	F	0	0	0	0	325	479

BLA 125504, ICC1300617/S002
 Cosentyx
 Prefilled Syringe and Autoinjector to deliver Cosentyx

Table 8: Skin Reaction Scores and Animal Weights (Oil Extraction)

Animal Number		24 Hour Score		48 Hour Score		Weight (g)	
Test Group	Sex	Test	Control	Test	Control	Pre-Test	Post-Test
10302	M	0	0	0	0	466	626
10303	M	1*	1*	1*	1*	463	598
10304	M	0	0	0	0	480	613
10305	M	0	0	0	0	412	524
10306	M	0	0	0	0	430	542
10307	M	0	0	0	0	407	532
10347	F	0	0	0	0	366	424
10348	F	0	0	0	0	323	410
10326	F	0	0	0	0	327	455
10327	F	0	0	0	0	323	423
10329	F	0	0	0	0	310	450
10330	F	0	0	0	0	320	420
Negative Control Group							
10308	M	0	0	0	0	436	584
10309	M	0	0	0	0	430	559
10310	M	1*	1*	1*	1*	490	680
10331	F	0	0	0	0	319	415
10332	F	0	0	0	0	327	434
10333	F	0	0	0	0	330	439

Table 9: Skin Reaction Scores and Animal Weights (Data from Historical Positive Control Study)

Animal Number		24 Hour Score		48 Hour Score		Weight (g)	
Test Group	Sex	Test	Control	Test	Control	Pre-Test	Post-Test
10182	M	3	0	3	0	400	533
10183	M	2	0	2	0	441	572
10184	M	3	0	3	0	435	481
10185	M	2	0	3	0	428	518
10186	M	3	0	3	0	439	544
10187	M	2	0	3	0	423	539
Negative Control Group							
10188	M	0	0	0	0	411	468
10189	M	0	0	0	0	427	528
10190	M	0	0	0	0	458	575
10191	M	0	0	0	0	420	510
10192	M	0	0	0	0	415	520
10194	M	0	0	0	0	423	540

Conclusion: no sensitization potential for the test article.

Test: Irritation

Protocol: page 8-15, MAF (b) (4)

Acceptance criteria:

Reaction	Primary Irritation Score
Erythema and Eschar Formation	
No erythema	0
Very slight erythema (barely perceptible)	1
Well-defined erythema	2
Moderate erythema	3
Severe erythema (beet redness) to eschar formation preventing grading of erythema	4
Edema Formation	
No edema	0
Very slight edema (barely perceptible)	1
Well-defined edema (edges of area well-defined by definite raising)	2
Moderate edema (raised approximately 1 mm)	3
Severe edema (raised more than 1 mm and extending beyond exposure area)	4
Total possible score for irritation:	
	8

Table adopted from ISO 10993-10:2010: Biological Evaluation of Medical Devices – Tests for Irritation and Skin Sensitization

Table 2: Primary Irritation Index Response Categories in Rabbits

Response Category	Mean Score
Negligible	0 to 0.4
Slight	0.5 to 1.9
Moderate	2 to 4.9
Severe	5 to 8

Adopted from ISO 10993-10:2010: Biological Evaluation of Medical Devices – Tests for Irritation and Skin Sensitization.

Results:

BLA 125504, ICC1300617/S002
 Cosentyx
 Prefilled Syringe and Autoinjector to deliver Cosentyx

Table 5: Individual Erythema and Edema Scores (SCI Extraction)

Rabbit Number	Time	Test Sites				Control Sites			
		Erythema		Edema		Erythema		Edema	
		T1	T2	T1	T2	C1	C2	C1	C2
58075	1 Hour	0	0	0	0	0	0	0	0
58078		0	0	0	0	0	0	0	0
58079		0	0	0	0	0	0	0	0
58075	24 Hours	0	0	0	0	0	0	0	0
58078		0	0	0	0	0	0	0	0
58079		0	0	0	0	0	0	0	0
58075	48 Hours	0	0	0	0	0	0	0	0
58078		0	0	0	0	0	0	0	0
58079		0	0	0	0	0	0	0	0
58075	72 Hours	0	0	0	0	0	0	0	0
58078		0	0	0	0	0	0	0	0
58079		0	0	0	0	0	0	0	0

Table 6: Individual Erythema and Edema Scores (OIL Extraction)

Rabbit Number	Time	Test Sites				Control Sites			
		Erythema		Edema		Erythema		Edema	
		T1	T2	T1	T2	C1	C2	C1	C2
58140	1 Hour	1	1	0	0	1	1	0	0
58142		1	1	0	0	1	1	0	0
58151		0	0	0	0	0	0	0	0
58140	24 Hours	0	0	0	0	0	0	0	0
58142		1	1	0	0	1	1	0	0
58151		0	0	0	0	0	0	0	0
58140	48 Hours	0	0	0	0	0	0	0	0
58142		1	1	0	0	1	1	0	0
58151		0	0	0	0	0	0	0	0
58140	72 Hours	0	0	0	0	0	0	0	0
58142		1	1	0	0	1	1	0	0
58151		0	0	0	0	0	0	0	0

Table 7: Primary Irritation Scores and Primary Irritation Index (SCI Extraction)

Rabbit Number	Sex	Weight (kg)	Primary Irritation Scores per animal	
			Test	Control
58075	M	2.6	0	0
58078	M	2.8	0	0
58079	M	2.5	0	0
Primary Irritation Index: (Total of Primary Irritation Scores divided by 3)			0	0
Overall Primary Irritation Index (Test-Control):			0	
Response Category:			Negligible	

Table 8: Primary Irritation Scores and Primary Irritation Index (OIL Extraction)

Rabbit Number	Sex	Weight (kg)	Primary Irritation Scores per animal	
			Test	Control
58140	F	2.1	0	0
58142	F	2.3	1	1
58151	F	2.3	0	0
Primary Irritation Index: (Total of Primary Irritation Scores divided by 3)			0.33	0.33
Overall Primary Irritation Index (Test-Control):			0	
Response Category:			Negligible	

Conclusion: The irritation response was classified as negligible.

Reviewer Comment: The MAF holder has provided the appropriate biocompatibility testing. Based on the review of the testing (cytotoxicity, sensitization, and irritation testing), the test results look acceptable. I have no further questions.

Sterilization

Evaluation of sterilization will be addressed by CDER.

Shelf Life/Accelerated Aging

The shelf life of the (b) (4) Auto-injector is based upon accelerated aging studies using the Arrhenius Reaction Rate Law. The Arrhenius Reaction Rate Law is commonly used in aging studies for polymer-based devices. Further detail of the Arrhenius Reaction Rate Law and the aging test protocol can be found in Attachment 8.

3.1 Non-aged samples test

Test environment	Output	DIR item	Test document #	Test item	Amounts
Non-aged samples for reference	Refer to test item	N/A	0154-002-TI-F01362	Test 9, 13, 14	See amounts below

3.2 Test No. 1 test items

Item	Test environment	Output	DIR item	Test document #	Test item	Amounts
Test No. 1.1	(b) (4)	N/A	DIR 8.1	N/A	Visual examination of components	See amounts below
Test No. 1.2	(b) (4)	Refer to test item	DIR 8.2	ISO/FDIS 11608-1 (N192); 0154-002-TI-C014e01 0154-002-TI-F002f02 0154-002-TI-F006e02 0154-002-TI-F006e01	Test 5, 11, 13-14, 18-19 (refer to pre-verification protocols 0154-002-SPVTP-110711, 0154-004-SPVTP-112124)	
Test No. 1.3	(b) (4)	Refer to test item	DIR 8.3	0154-002-TI-C004e01 0154-002-TI-C005e01 0154-002-TI-C006e01 0154-002-TI-C007e01 0154-002-TI-F001f03 0154-002-TI-F002f02 0154-002-TI-F004f02 0154-002-TI-F006e01 0154-002-TI-F009e01	Examination according to attribute test procedure (Test 21) Test 1-4, 6, 9, 11, 18-19 (refer to pre-verification protocols 0154-002-SPVTP-110711, 0154-004-SPVTP-112124)	

3.3 Test No.2 test items

Item	Test environment	Output	DIR item	Test document #	Test item	Amounts
Test No. 2.1	(b) (4)	N/A	DIR 8.2	ISO/FDIS 11608-1 (N192); 0154-002-TI-C013 0154-002-TI-F002f02 0154-002-TI-F004f02 0154-002-TI-F006e01	Tests 5, 11, 13-14, 18-19 (refer to pre-verification protocols 0154-002-SPVTP-110711, 0154-004-SPVTP-112124)	See amounts below
Test No. 2.2	(b) (4)	Refer to test item	DIR 8.3	0154-002-TI-C004e01 0154-002-TI-C005e01 0154-002-TI-C006e01 0154-002-TI-C007e01 0154-002-TI-F001f03 0154-001-TI-F002f02 0154-002-TI-F004f02 0154-002-TI-F006e01 0154-002-TI-F009e01	Examination according to attribute test procedure (Test 21) Test 1-4, 6, 9, 11, 18-19 (refer to pre-verification protocols 0154-002-SPVTP-110711, 0154-004-SPVTP-112124)	

Based on the conclusion of the sponsor, (b) (4) Components, sub-assemblies of Front and Rear sub-assemblies and finally assembled devices have been exposed to accelerate ageing corresponding to the maximum storage time in sequence ((b) (4)), followed by testing according to the Accelerated ageing test protocol 0154-004-ATP-20120217-A. (The acceleration calculation is based on the Arrhenius Reaction Rate Function theory and the ASTM3045 related rules as reference).

Reviewer Note: Based on review of this information, it appears that all durability requirements specified in Accelerated ageing test protocol were successfully fulfilled. As a result, I have no further questions.

Functional Testing

(b) (4) has conducted bench testing to demonstrate the functionality and reliability of (b) (4) auto-injector, which includes function test, attribute test and component test based on the design input requirements of the (b) (4) auto-injector. The function test and attribute test were performed using the final assembled (b) (4) with the pre-filled

syringe. The assessment for the completion of user sequence was demonstrated by attribute test for which the (b) (4) was manually activated using an injection pad. The test summary and result are provided in Table 4 and Attachment 7.

Table 4. Summary of the Design Verification Test Results

Type of Test	Test Description	Acceptance Criteria	Results
Functional Tests:			
Cap removal torque	Measure the peak torque needed to rotate the cap and the shield remover from the injector. Final assembled device excluding the label	(b) (4)	Pass
Activation force	Measure the force on the needle cover to trigger actuation	(b) (4)	Pass
Needle cover displacement at activation	Measure the displacement of the needle cover before actuation	(b) (4)	Pass
Dose accuracy	Weigh the mass expelled from the pre-filled syringe to ensure that the drug was expelled completely during injection. When volume is not sufficient, perform COIS test.	(b) (4)	Pass
Needle Extension	Measure the needle length exposed during injection	(b) (4)	Pass
Needle cover safety, displacement at 80 N	Verify that the force greater than or equals to 80 N load cannot push the needle cover back into the front subassembly after injection, and the needle cannot be seen after the needle cover withstood 80 N force. (The needle cover is exposed to a force of min 10 N before this test.)	(b) (4)	Pass

3.1 Component tests

Item	Test item	Output/unit	DIR item	Test document#	Specification limit	Amounts
Test 1A	Rear end cover and front shell separation force	N	DIR 2.8	0154-002-TT-C00401	(b) (4)	60 pcs
Test 1B	Rear end cover and front shell separation force	N	DIR 2.8	0154-002-TT-C00401	Refer to (b) (4) aging protocol ATP20120217	
Test 2A	Front end cover and front shell separation force	N	DIR 2.9	0154-002-TT-C00501	(b) (4)	60 pcs
Test 2B	Front end cover and front shell separation force	N	DIR 2.9	0154-002-TT-C00501	Refer to (b) (4) aging protocol ATP20120217	
Test 3	Cap and RNS remover separation force	N	DIR 2.15	0154-002-TT-C00601	(b) (4)	60 pcs
Test 4	Shield remover removal force	N	DIR 2.16	0154-002-TT-C00701	(b) (4)	60 pcs
Test 5	Cap pull off force from front end cover	N	DIR 2.20	0154-002-TT-C01401	(b) (4)	60 pcs

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Item	Test item	Output/unit	DIR item	Test document#	Specification limit	Amounts
Test 6	Visual inspection of drug product	Pass/Fail	DIR 2.14	0154-002-TT-F011 #01	(b) (4)	10 pcs

Item	Test item	Output/unit	DIR item	Test document#	Specification limit	Amounts
Test 7	Total weight	g	DIR 2.24	0154-002-TT-F012 #01	(b) (4)	30 pcs
Test 8	Injector measurement	mm	DIR 2.25	N/A	(b) (4)	30 pcs

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Item	Test Item	Output/ unit	DIR Item	Test document#	Specification limit	Amounts
Test 9	Cap removal torque	Nm	DIR 2.19	0154-002-TI-F013 #01	(b) (4)	60 pcs with label
Test 10	RNS vs. Cap movement	Pass/Fail	DIR 2.17	0154-002-TI-F014 #01	(b) (4)	60 pcs

Item	Test Item	Output/ unit	DIR Item	Test document#	Specification limit	Amounts
Test 11	Activation force	N	DIR 2.6	0154-002-TI-F005#02	(b) (4)	60 pcs
Test 12	Needle cover displacement at activation	mm	DIR 2.4	0154-002-TI-F002#02	(b) (4)	
Test 13	Injection time	second	DIR 2.1	0154-002-TI-F002#02	(b) (4)	

Item	Test Item	Output/ unit	DIR Item	Test document#	Specification limit	Amounts
Test 14	Dose accuracy	ml	DIR 2.2	0154-002-TI-F002#02	(b) (4)	60 pcs
Test 15	Injection depth	mm	DIR 2.3	0154-002-TI-F002#02	(b) (4)	

Item	Test Item	Output/ unit	DIR Item	Test document#	Specification limit	Amounts
Test 16	Needle cover distance	mm	DIR 2.5	0154-002-TI-F003 #01	(b) (4)	60 pcs
Test 17	Front end cover attached after use	mm	N/A	0154-002-TI-F007 #01	(b) (4)	60 pcs

Item	Test Item	Output/ unit	DIR Item	Test document#	Specification limit	Amounts
Test 18	Needle cover safety, displacement at 80N	mm	DIR 2.7	0154-002-TI-F004#02	(b) (4)	60 pcs
Test 19	Rear end cover displacement at 190N	mm	DIR 2.8	0154-002-TI-F006 #01	(b) (4)	

Item	Test Item	Output/ unit	DIR Item	Test document#	Specification limit	Amounts
Test 21	Attribute test	Pass/Fail	DIR 2.10, 2.11, 2.12, 2.13, 2.18, 2.26, 2.24 and 2.35	0154-002-TI-F009 #01	(b) (4)	125 pcs (with device label attached) with API filled syringe and 125 pcs with WFI filled syringe

Item	Test Item	Output/ unit	DIR Item	Test document#	Specification limit	Amounts
Test 22	Assessment by project team	Pass/Fail	DIR 2.10, 2.11, 2.12, 2.13, 2.18, 2.21, 2.23, 2.28, 2.29, 2.30, 2.31, 2.32, 2.33, 2.34, 2.2, 3.3	0154-002-TI-F009#01	(b) (4)	5 pcs or as required

Item	Test Item	Output	DIR Item	Test document#	Specification limit	Amounts
Test 23	Transportation test procedure	ISTA 2A Pass/Fail	DIR 6.1	ISTA 2A	(b) (4)	210 pcs for front subconnector (1 box)/360 pcs for rear subconnector (1 box)

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					(b) (4)	
	Dose accuracy	nil		0154-002-T1-F002-02		50pcs lines transportation injections
	Injection time	second		0154-002-T1-F002-02		50pcs lines transportation injections

Item	Test item	Output	DER item	Test document #	Specification limit	Assessm
23	Three direction	Pass/Fail		ISO/FDIS 11608-1 (N198) (2011-06-29)	(b) (4)	
24	Device drop test		DER 6.2			60 pcs (with label)
	Dose accuracy	nil		0154-002-T1-F002-02		

3.14 Biocompatibility test

Item	Test item	Output	DER item	Test document #	Specification limit	Assessm
25	All materials in contact with the user shall comply with EN ISO 10993-1:2009 biological evaluation of medical devices	Pass/Fail	DER 3.1	ISO 10993-1:2009 for processes and for critical and non-critical areas	(b) (4)	Assessm as decided in the (b) (4)
26	Basic materials - normal origin contact product must minimize BSE/TSE	Supplier Certificate	DER 3.4	TSE guidelines, BSE/TSE control, etc. 2002/35/EC and 2003/182/EC Directive 2003/86/EC		Preparation for biocompatibility testing

3.15 Usage environmental requirements

Item	Test item	Output	DER item	Test document #	Test item	Assessm
27	Injection shall be completed for standard atmosphere (18 to +28 °C, 25-75 %RH) (Storage at 21 °C at least for 4 hours)	Second	DER 7.1	ISO/FDIS 11608-1 (N198) (2011-06-29) 0154-002-T1-F002-02	(b) (4)	60 pcs
28	Injection shall be completed for cold atmosphere (5 to +21 °C, Storage at 9 °C at least for 4 hours)	Second	DER 7.2	ISO/FDIS 11608-1 (N198) (2011-06-29) 0154-002-T1-F002-02		60 pcs

3.16 Durability requirements

Item	Test environment	Output	DER item	Test document #	Test item	Assessm
29	(b) (4)	N/A	DER 8.1	N/A	(b) (4)	
30	(b) (4)	N/A	DER 8.2	ISO/FDIS 11608-1 (N198) (2011-06-29) 0154-002-T1-F002-02; 0154-002-T1-F002-02; 0154-002-T1-F002-02; 0154-002-T1-F002-02		Refer to accelerated aging protocol no. A.PP20120217
31	(b) (4)	Refer to test item	DER 8.3	ISO/FDIS 11608-1 (N198) (2011-06-29) 0154-002-T1-F002-02; 0154-002-T1-F002-02; 0154-002-T1-F002-02; 0154-002-T1-F002-02		

3.17 Storage environmental test

Item	Test environment	Output	DER item	Test document #	Test item	Assessm
32	(b) (4)		DER 9.1	ISO/FDIS 11608-1 (N198) (2011-06-29) 0154-002-T1-F002-02	(b) (4)	60 pcs
33	(b) (4)	Refer to test item	DER 9.4	ISO/FDIS 11608-1 (N198) (2011-06-29) 0154-002-T1-F002-02		60 pcs
34	(b) (4)		DER 9.5	ISO/FDIS 11608-1 (N198) (2011-06-29) 0154-002-T1-F002-02		60 pcs

3.18 Syringe total length measurement					
Item	Test Item	Output	DIR Item	Test document#	Specifications
Test 29	Syringe total length before and after assembly	mm	DIR 2.22, 2.23	0194-002-19-010101	(b) (4)

Complete test results are found on page 229-302

Dose Accuracy Testing

The (b) (4) test for dose accuracy is a measurement of delivered volume and assessment of completeness-of-injection. Dose accuracy is operationally defined by (b) (4) as the expelling of the labeled volume (or greater) from the prefilled syringe. Although (b) (4) uses the term "dose accuracy" in some documents, (b) (4) does not evaluate dose accuracy, which is a function of the ability to set a dose, and for a single use injector the volume of dose expelled is dependent upon the actual fill volume of the syringe. The delivered volume tested by (b) (4) does compare the expelled volume to the labeled volume of the syringe, and there is a visual confirmation of the travel of the plunger rod that a complete forward movement of the injection plunger rod has occurred.

Reviewer Note: The sponsor provided testing for 29 tests to address the functionality of the device component. Review of this testing showed that several components of the design verification testing failed based on the result provided in the design verification test report. The following tests failed based on the report:

- a. The RNS rotation at cap removal
- b. Dose accuracy from old syringe batch Y0680711
- c. Horizontal direction drop dose accuracy old syringe batch Y0680711
- d. Cap downward dose accuracy old syringe batch Y0680711
- e. Dose accuracy for old syringe batch at 40°C
- f. Dose accuracy after precondition old syringe batch (hot)
- g. Dose accuracy after precondition old syringe batch (cold)

Sponsor Justification:

1. *Dose accuracy: The Dose accuracy results were below the specification and consequently deemed Fail in the Tests 14-1, 23-1, 24-1, 24-9, 26-9, 28-1, 28-5, 28-9. These test results are denoted "old syringe batch Y0680711" in the report. The low dose accuracy is considered not a result of the auto-injector but rather due to too low fill volume. The customer provided a new syringe batch after correction of the fill volume (syringe batch no. S0002).*
2. *RNS vs Cap movement: The background of this test is to avoid risk of coring if the RNS is rotated against the needle, i.e. the needle cutting out a piece of rubber from the RNS, which could potentially be injected. The investigation showed that even with a limited rotation of the RNS towards the needle there is no coring. The sponsor concludes that the Design verification shows that the device fulfils the intention of the requirement, i.e. to ensure no coring. Their Proposed corrective action is to change the DIR requirement 2.17 updated as follows: Change from:*

To: " (b) (4)

(b) (4)

To further verify that the mitigation proposed by the sponsor was acceptable, I had Jason To, a biomedical engineer review the testing for adequacy. Based on the failures noted, the sponsor will need to provide a detailed justification and rationale as to how and why the drop tests are adequate in demonstrating the robustness of your device. Additionally, the sponsor will need to provide additional information regarding the safety constraints that you have implemented to mitigate dose accuracy testing that was below specifications from occurring in the field and provide evidence that these safety constraints are effective. Finally, the sponsor will need to provide a risk analysis identifying all possible hazards and risks associated with the occurrence noted in the design verification test report 0154-002-TR-F14-001 shows that the RNS rotates partly with the cap at removal, thus failing the design input requirement Based on our review of the information, the sponsor's justification for the failures in dose accuracy and RNS vs. cap movement is acceptable as incorrect fill volume could affect accuracy of dose and as the corrected fill volume resulted in a test pass, the result is satisfactory.

Packaging and Shipping

One cardboard shipping box containing each of Front or Rear subassemblies were tested to simulate a general distribution cycle including manual handling, stacked vibration, vehicle vibration, concentrated impact and manual handling per ASTM D4 J69-09 Standard Practice for Performance Testing of Shipping Containers and Systems.

Test: (b) (4) transportation validation activity

Protocol: Attachment 9 of MAF (b) (4)

Acceptance criteria

4 Test Item

Item	Test item	Output/ unit	DIR item	Test document#	Specification limit	Amounts
Test 1	At Novartis: Visual inspection of outer package (Carton including carton label). Results to be reported/filled in section 5 below	N/A	N/A	N/A	Package shall be intact and label fully intact/readable.	All cartons
Test 2	At (b) (4) upon return of the cartons to (b) (4) Visual inspection of cartons including label	N/A	N/A	N/A	Package shall be intact and label fully intact/readable.	All cartons

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Test 3	At (b) (4) upon return of the cartons to (b) (4) Visual inspection: Examine all samples with a (b) (4) reference	N/A	N/A	N/A	The (b) (4) shall be intact and not disengaged (b) (4) or deformed	All samples
Test 4	Injection time: (b) (4) (ACZ885 API) and (b) (4) (AIN457 API)	second	DIR 2.1	0154-002-TI-F002:02	(b) (4)	
Test 5	Dose accuracy	ml	DIR 2.2	0154-002-TI-F002:02	(b) (4)	30 pcs separately for AIN457 API, AIN457 placebo and ACZ885 API
Test 6	Injection time: (b) (4) (AIN457 placebo)	second	DIR 2.1	0154-002-TI-F002:02	(b) (4)	

Results:

Test 1 description	Specification limit	Novartis observation (to be manually filled in by inspector/s at Novartis)	Pass/Fail (to be manually filled in by inspector at Novartis)
At Novartis: Visual inspection of outer package (Carton including carton label).	Package shall be intact and label fully intact/readable.	Labels fully intact and readable. One carton appears damaged and another carton appearance transformed a little.	Pass
Name/ function of inspector/s at Novartis	Date and place:	Signature:	(b) (4)

Test 2 description	Specification limit	(b) (4) observation (to be manually filled in by inspector/s at (b) (4))	Pass/Fail (to be manually filled in by inspector/s at (b) (4))
At (b) (4) upon return of the cartons to (b) (4) Visual inspection of carton including label	Package shall be intact and label fully intact/readable.	Labels fully intact and readable. One carton appearance damaged and another carton appearance transformed a little.	Pass
Name/ function of inspector/s at (b) (4)	Date and place	Signature	(b) (4)

Test 3 description	Specification limit	SHL observation (to be manually filled in by inspector/s at (b) (4))	Pass/Fail (to be manually filled in by inspector/s at (b) (4))
At (b) (4) upon return of the cartons to (b) (4) Visual inspection: Examine all samples with a good (b) (4) and a (b) (4) as reference	The (b) (4) shall be intact and not disengaged (b) (4) or deformed	The (b) (4) are intact and not disengaged (b) (4) or deformed.	Pass
Name/ function of inspector/s at (b) (4)	Date and place	Signature	(b) (4)

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(b) (4) ejection time specification (Specification limit, (b) (4))

Sample#	Value (unit: sec)
1	10.0
2	9.2
3	10.0
4	10.3
5	9.3
6	9.0
7	9.6
8	8.7
9	8.7
10	8.9
11	8.5
12	8.9
13	9.5
14	9.4
15	8.5
16	10.1
17	9.7
18	9.7
19	9.9
20	9.5
21	11.1
22	9.3
23	10.7
24	10.1
25	10.3
26	10.2
27	10.0
28	10.3
29	8.9

30	8.7
Mean value	9.1
Max. Value	11
Min. Value	8
St. Dev.	0.67

(b) (4) ejection time specification (Specification limit, (b) (4))

Sample#	Value (unit: sec)
1	8.8
2	9.0
3	8.4
4	8.4
5	9.6
6	9.4
7	9.3
8	9.1
9	7.9
10	8.3
11	9.5
12	9.4
13	9.1
14	11.8
15	9.0
16	9.4
17	7.9
18	9.7
19	8.7
20	7.7
21	8.2

22	8.6
23	8.6
24	8.9
25	8.1
26	8.5
27	7.7
28	8.8
29	9.4
30	8.6
Mean value	8.9
Max. Value	12
Min. Value	8
St. Dev.	0.80

(b) (4) net result: dose accuracy specification (Specification limit, (b) (4))

Sample #	Value (unit: ml)
1	0.974
2	0.972
3	0.979
4	0.982
5	0.981
6	0.979
7	0.977
8	0.969
9	0.974

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10	0.982
11	0.985
12	0.980
13	0.976
14	0.981
15	0.975
16	0.989
17	0.985
18	0.972
19	0.980
20	0.984
21	0.990
22	0.982
23	0.979
24	0.976
25	0.973
26	0.993
27	0.984
28	0.973
29	0.966
30	0.978
Mean value	0.9790
Max. Value	0.993
Min. Value	0.966
St. Dev.	0.0061

N=30, X=0.979, S=0.0061, k=2.220

condition 1: $V_{\text{act}}=(0.979-(2.22*0.0061))=0.966 > L=0.950$ (pass)

condition 2: $k_{\text{act}}=(0.979-0.95)/0.0061=4.754 > k=2.220$ (pass)

(b) (4) test result: dose accuracy specification (Specification limit, V_{act} (b) (4) with

Sample #	Value (unit: ml)
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1	1.005
2	0.996
3	0.997
4	0.998
5	0.997
6	0.993
7	1.007
8	0.997
9	1.006
10	1.002
11	0.994
12	1.001
13	1.010
14	0.991
15	1.001
16	0.996
17	0.991
18	1.001
19	0.992
20	0.995
21	0.987
22	0.990
23	1.001
24	0.999
25	0.992
26	1.001
27	0.997
28	1.001
29	0.985
30	1.005
Mean value	0.9975
Max. Value	1.010
Min. Value	0.985
St. Dev.	0.0060

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(N=30, X=0.998, S=0.0060, k=2.220)
 condition 1: $Vest=(0.998-(2.220*0.0060))=0.985 > L=0.950$ (Pass)
 condition 2: $kact=(0.998-0.95)/0.0060=8.000 > k=2.220$ (Pass)

(b) (4) test result: dose accuracy specification (Specification limit, Vest (b) (4) (with p=0.950))

Sample #	Value (unit: ml)
1	1.000
2	0.997
3	0.996
4	0.988
5	0.998
6	0.998
7	0.997
8	0.993
9	0.990
10	0.997
11	0.990
12	0.981
13	0.980
14	0.991
15	1.004
16	0.991
17	0.997
18	0.990
19	0.996
20	0.997
21	1.006
22	0.998
23	0.993
24	0.982
25	0.992

(b) (4) injection time specification (Specification limit, (b) (4))

(b)

Sample#	Value (unit: sec)
1	4.6
2	4.8
3	5.1
4	5.2
5	5.8
6	8.2
7	5.0
8	4.9
9	4.6
10	4.7
11	5.2
12	5.2
13	5.4

14	5.8
15	6.5
16	6.1
17	6.7
18	4.6
19	4.9
20	4.8
21	6.0
22	6.0
23	5.9
24	5.8
25	6.6
26	5.6
27	5.0
28	5.6
29	4.9
30	4.7
Mean value	5.5
Max. Value	8
Min. Value	5
St. Dev.	0.81

Conclusion: All testing passed.

Reviewer notes: The sponsor indicated that there was some minor damage on the outer packaging after the transport from Novartis, Basel to (b) (4) but according to the sponsorthis did not impact the subassemblies and this level of damage is not considered a risk for the subassembly quality. Based on the results of the testing and lack of failures, I would agree with the assessment. I have no further questions.

Labeling/IFU and usability for PFS and Auto Injector

Regarding instructions for use, CDRH Device Evaluation defers to the human factor teams to evaluate the validity of the instructions for use.

Per LCDR Quynh Nguyen's consult, the human factors validation study for the autoinjector configuration was conducted with 165 participants representing the intended users. Of these, 94 participants received realistic, predefined training and returned for a simulated use assessment session either one week or four weeks after their training; and 71 participants were untrained and carried out their simulated use assessment without support.

During the first unsupervised injection:

- Seven (7/94) trained participants did not complete the injection successfully due to failure to activate the (b) (4) AI, to hold the (b) (4) AI against the injection site until the 2nd 'click' (5 instances), and due to moderator intervention (two instances) to prevent possible needle stick injuries (identifying the correct end of the pen to perform injection)
- Six (6/71) untrained participants failed to deliver their first unsupervised injection due to failure to hold the (b) (4) AI against the injection site until the 2nd 'click'. During the one week and four week assessments, two (2/56) and five (5/38) trained participants failed to perform the injection respectively due to failure to hold the (b) (4) AI against the injection site until the 2nd 'click.' These results were intended to demonstrate user performance after some time has elapsed between receiving training and performing the next injection. In addition, there were 20/165 participants (trained and untrained) experienced difficulty but were able to successfully complete an injection. These difficulties were due to:
 - Green Plunger Confusion: Confusion over the appearance or the motion (e.g. direction or speed) of the (b) (4) AI's green plunger.
 - Confusion over how to activate the injection: tried to activate the (b) (4) AI by pressing a button rather than pushing down on the device body to trigger the injection (1st 'click').
 - Inadvertent 2nd 'click' removal: when the mechanism activated on the 2nd 'click', the injector 'sprang-up' out of the participant's hand as they applied insufficient grip and downward force to the injector to keep it in place. Participants therefore received a 'clinically effective' albeit 'wet' injection
 - Struggle to maintain downward pressure: struggled to keep the (b) (4) AI pressed firmly against the skin until the 2nd 'click' was heard and the green plunger had stopped moving. Several modifications to the Instructions for Use have been made to address the task failures associated with the 2nd click issue.

Reviewer Note: LCDR Quynh Nguyen was consulted by CDER to evaluate the usability including the instructions for use for the device. Based on her evaluation, she found the study results and analyses acceptable. Given the nature of the proposed IFU changes, LCDR Nguyen does not believe that additional human factors validation study is needed.

5. CDRH ODE Device Evaluation Recommendations

On February 20, 2014, CDRH ODE asked CDER ONDQA to send a request for additional information to the authorized representative for MAF (b) (4). CDRH ODE has reviewed the proposed packaging and has no concerns regarding the adequacy of package labeling.

A separate consult should be sent to CDRH Office of Compliance regarding the possible need for a facilities inspection.

On February 20, 2014, the following request for additional information was sent to CDER to request additional information of the MAF holder for the (b) (4) injector. MAF requests for additional information are sent through CDER ONDQA.

MAF (b) (4)
(b) (4)

1. 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.

Sponsor's response:

(b) (4) Response:

Please be advised that the sponsor, Novartis, performed the test of sharps injury prevention feature with a simulated clinical use test in accordance to the FDA Guidance for Industry and FDA Staff- Medical Devices with Sharps Injury Prevention Features, 2005. The results are summarized in the sponsor's BLA #125504 for Cosentyx 150 mg/1 ml solution for injection in prefilled autoinjector/pen.

In addition to the testing conducted by the Sponsor, (b) (4) successfully performed testing on the (b) (4) Auto Injector device to ensure functionality and robustness of the sharps injury prevention feature. This test, the Needle Cover Safety Displacement (shield override force) at 80 N, was performed within the verification that a force greater than or equal to 80 N load cannot push the needle cover back into the front subassembly after injection. The safety distance to the needle remains and the needle cannot be seen after the needle cover withstood 80 N of force. The results indicated that the device successfully met the requirements.

The full description of this and all Design Verification Protocol and Report were provided in Attachment 7 of the original MAF (b) (4) received by FDA on June 4, 2013.

CDRH response: The MAF holder has stated that the needlestick prevention feature testing was completed by the BLA holder. The BLA holder was contacted on April 24, 2014 to verify where specifically this information could be found.

Reviewer’s Note: CDER spoke with Novartis and this information is located in module 3.2.P Drug Product under the “pen” folder. It is under “3.2.P.2 Pharmaceutical Development” in a file titled “pharmaceutical-development-appendix”. The autoinjector module references the PFS module. The PFS information is under the “prefilled syringe” folder. It is under “3.2.P.2 Pharmaceutical Development” in a file titled “pharmaceutical-development-appendix”. Review of the documents cited is as follows:

Simulated Use Design: Design Verification of the proposed marketed product configuration of the PFS with (b) (4) safety device was performed to ensure the design outputs conformed to design input requirements. Since there was no device development performed by Novartis for each supplied component, and as verification of each supplied component was performed by the supplier, only design verification specific to the combination of PFS with (b) (4) safety device was performed.

Sample size-500 (b) (4) activations were attempted and successfully completed based on FDA recommendations in guidance document “Medical Devices with Sharp Injury Prevention Features” by 35 subjects comprised of the following:

- n=5 healthcare professionals
- n=21 patients
- n=6 caregivers who are responsible for assisting a friend or family member to take medication
- n=2 adolescents

Test protocol: Verification of requirements:

Table 3-4 Verification of PFS with (b) (4) safety device

Test No.	Test Item	Design Input	Test Method	Acceptance Criteria	Results
Verification of requirements specific to the combination of PFS with (b) (4)					
1	The PFS with safety device is suitable for subcutaneous injection with a 1 ml long ISO standard glass syringe with a 1/2" long staked needle	DIR1.1	Paper check	(b) (4)	PASS
2	The PFS with safety device is suitable for users from age (b) (4) years and older	DIR1.2	Paper check	(b) (4)	PASS
3	The PFS with safety device can be activated with only one hand	DIR1.3	Paper check	(b) (4)	PASS
4	The selection of off-the-shelf components must ensure that the PFS with safety device is suitable for both right hand as well as left hand use	DIR1.4	Paper check	(b) (4)	PASS
5	Different colors of the (b) (4) as defined per component specification shall be used to identify the content of the syringe	DIR1.5	Visual inspection	(b) (4)	PASS
6	The PFS with safety device provides a shelf life of at least (b) (4) at storage temperature of 2-8°C	DIR1.7	Visual inspection and Stability study	(b) (4)	PASS
7	The safety device is suitable for the use with a 1 ml long ISO standard (b) (4) syringe	DIR1.8	Paper check	(b) (4)	PASS
8	The safety device prevents needle stick injuries	DIR1.1	Paper check	(b) (4)	PASS
9	The safety feature does not activate prior to the end of the injection	DIR1.2	Paper check	(b) (4)	PASS
10	The user can check the drug product integrity and the label of the syringe	DIR1.3	Paper check	(b) (4)	PASS

Results: Zero (0) failures of the (b) (4) were observed meeting the requirement for 500 successful activations of the device.

*Conclusion: Pre-filled syringe with (b) (4) had no failures of the needle stick prevention feature. **The sponsor's response to this deficiency is acceptable.***

On April 23, 2014 the following request for additional information was sent to CDER to request additional information of the MAF holder for the (b) (4) injector. MAF requests for additional information are sent through CDER ONDQA with a requested completion date of May 5, 2014:

MAF (b) (4)
(b) (4)

- 1) You performed drop testing on your device to demonstrate its robustness. However, please note that drop testing should be performed with samples that are representative of the final finished device, including identical weight and contents requirements, from a height that is fully representative of the actual use of the device in the field onto a hard surface to demonstrate worst case bounds. Please provide a detailed justification and rationale as to how and why your drop tests are adequate in demonstrating the robustness of your device. Please note that based on your response, additional information may be required.

Sponsor Response: Drop testing for the (b) (4) Autoinjector was performed in accordance to ISO 11608-1:2012, Needle-based injection systems for medical use –Requirements and test methods, section 10.5, Free-fall testing. This ISO standard is recommended to be followed in the FDA guidance document, *Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products, June 2013*. The devices used for this testing were samples that are representative of the final finished commercial device including weight, color and components. All components used in the assembly of the device were from validated tooling. ISO-11608-1:2012, Needle-based injection systems for medical use –Requirements and test methods requires the 30 samples (10 devices dropped in three different configurations). However, (b) (4) performed the testing using 60 devices. Three sets of 20 devices were dropped horizontally, vertically with the device cap up and vertically with the cap down. They were dropped from a height of 1000 mm onto a test surface in accordance with the ISO-11608-1:2012, Needle-based injection systems for medical use–Requirements and test methods. Visual inspection for any defects, followed by dose accuracy testing was successfully performed on all 60

samples. Based on these results, (b) (4) concluded that the (b) (4) autoinjector successfully met the Free-fall Testing (drop test) requirements of ISO 11608-1:2012, Needle-based injection systems for medical use –Requirements and test methods. The full description of this and all Design Verification Protocol and Report were provided in Attachment 7 of the original MAF (b) (4) received by FDA on June 4, 2013.

CDRH Response: *The sponsor states that drop testing for the device was performed in accordance to ISO 11608-1:2012, section 10.5, Free-fall testing, and that the devices used for this testing were samples that are representative of the final finished commercial device including weight, color and components. The firm performed this testing using 60 devices. Three sets of 20 devices were dropped horizontally, vertically with the device cap up and vertically with the cap down. They were dropped from a height of 1 meter. The sponsor reports that visual inspection for any defects, followed by dose accuracy testing was successfully performed on all 60 samples. The response is acceptable.*

- 2) You provided dose accuracy testing in which the results were below specifications. You state that the low dose accuracy was considered not a result of the auto-injector device but rather due to low fill volume, and a new batch was tested to provide successful results. However, this issue poses a risk should it occur in the field with the end user that has your device with a low fill volume. Thus, please provide additional information regarding the safety constraints that you have implemented to mitigate this issue from occurring in the field and provide evidence that these safety constraints are effective. Please note that based on your response, additional information may be required.

Sponsor Response: *The (b) (4) Autoinjector is designed to expel the entire contents of a pre-filled syringe. Therefore, dose accuracy is controlled by the sponsor's (b) (4). Please note below, the sponsor has provided the explanation of the fill process for the primary container intended for use with this device: During the manufacturing process of the Secukinumab Pre Filled Syringe (PFS) (b) (4)*

As a consequence, the dose accuracy requirements were not met during design verification testing. In batch S0002 (885277) that was used for the second design verification experiment, the average fill weight was observed to be at the target fill weight and the dose accuracy requirements were met during design verification testing. Page 3 of 5 In order to improve the statistical distribution of the dose accuracy data to more closely meet the target specification, the overfill of the PFS was increased from (b) (4) as described in detail in in the sponsor's application, BLA 125504 for Cosentyx 150

mg/1 ml Solution for injection in prefilled syringe, Module 3.2.P.2 (eCTD filename: pharmaceutical-development), section 2.2.1. This change supports an improved product performance by more robustly meeting the target of the specification for dose accuracy of (b) (4) mL. Furthermore, the acceptable fill weight range was tightened from (b) (4) %. Figure 1 depicts dose accuracy results from AIN457 150 mg/1mL Solution for injection in pre-filled autoinjector batches manufactured with the original and the adapted overfill. Based on the increase in overfill during the filling process, the occurrence of low fill of the PFS has been mitigated. Please refer to the sponsor's BLA #125504 for Cosentyx 150 mg/1 ml solution for injection in prefilled autoinjector/pen for more information.

CDRH Response: The sponsor asserts that during the manufacturing process of the Secukinumab Pre Filled Syringe (PFS), (b) (4)

(b) (4)
Thus, the dose accuracy requirements were not met during design verification testing. In batch S0002 (885277) that was used for the second design verification experiment, the average fill weight was observed to be at the target fill weight and the dose accuracy requirements were met during design verification testing. The sponsor increased the overfill of the PFS from (b) (4). The firm states that this is described in the sponsor's application, BLA 125504 for Cosentyx 150 mg/1 ml Solution for injection in prefilled syringe, Module 3.2.P.2 (eCTD filename: pharmaceutical-development), section 2.2.1. Furthermore, the acceptable fill weight range was tightened from (b) (4) %. The sponsor's response is incomplete. **The sponsor's response is not acceptable.**

As a result, the following IR was sent to the sponsor relating to this matter on May 12, 2014:

You provided a response to FDA question #2 on May 2, 2014 regarding dose accuracy testing that showed results that were below specifications. In this response, you assert that this occurrence was due to low fill volume caused by the fill process. In batch Y068 0711, you state that the average fill weight was observed to be slightly below the target fill weight, and therefore caused results below dose accuracy requirements. Please verify and confirm that the devices in batch Y068 0711 expelled the entire contents of the pre-filled syringe, as your autoinjector is designed to accomplish.

Sponsor Response: The (b) (4) Autoinjector is designed to expel the entire contents of a pre-filled syringe. The devices used during the initial design

verification testing with syringe batch Y068 0711 did function as intended by expelling the entire contents of the pre-filled syringe.

CDRH Response: *The sponsor has confirmed that their device expels the entire contents of the pre-filled syringe. The response is acceptable.*

- 3) Design verification test report 0154-002-TR-F14-001 shows that the RNS rotates partly with the cap at removal, thus failing the design input requirement. You state that the purpose of this test is to avoid the risk of coring and thus, performed an investigation and testing to show that no coring would occur. However, it is not clear if there are any additional risks that are associated with this phenomenon, in which the RNS rotates with the cap at removal. Please provide a risk analysis identifying all possible hazards and risks associated with this occurrence. Describe the safety measures that you have implemented to mitigate these hazards and risks and explain how and why they are effective. Please note that based on your response, additional information may be required.

Sponsor Response: *The Design Input requirement for the (b)(4) device reads: “When the Cap is twisted off from the device the syringe RNS shall not rotate”. Ref Doc No 0154-002-IR-IR-S002, rev. D, item #2.17. The corresponding User Requirement Specification reads: “The device must provide means of easy and secure removal of the RNS from the syringe”. Ref. Doc. No AIN457_URS (b)(4) (b)(4), URQ item 1.13. As described in the Design verification report 0154-004-DVTR-B (Test 10) and the Design verification report 0154-002-TR-F14-001, it was concluded that that the RNS rotates partly with the cap at removal, thus failing the design input requirement. As a consequence, there was a Risk Assessment performed with the purpose of assessing risks related to safe removal of the RNS from the syringe when the Cap is twisted off from the (b)(4) device. In summary the Risk assessment cover the potential risk of coring. Two potential effects were identified; a) risk of blockage of the needle causing No dose and b) risk of Injection of drug containing particulates. Both risks were evaluated .No additional risks have been identified during the risk assessment. In the Risk assessment there is a description of the (b)(4) design, which explains the restrictions (safety measure) to rotation of the needle shield (through the Cap removal) versus the Needle: (b)(4)*

Additionally to the risk assessment a testing was performed on pre-filled syringes as well as on devices in which the Needle shield was rotated against the Needle to the worst theoretical degree (65 degrees angle) in order to support the fact that such degree of rotation does not expose any risk of coring (= cut out of small rubber piece). Test result summary: In summary, there was no coring detected in the test which was conducted on 250 pre-filled syringes and 60 devices. The Risk assessment Doc. No. 0154-002-RM-S008 can be found as Attachment 1 of this response. It is (b)(4) opinion that the additional verification testing and risk

evaluation has adequately addressed the inquiry. oughout the total angular movement of approximately 65 degrees.

CDRH Response: *The sponsor states that a Risk Assessment performed with the purpose of assessing risks related to safe removal of the RNS from the syringe when the Cap is twisted off from the device. The sponsor states that the Risk assessment cover the potential risk of coring, and that two potential effects were identified: a) risk of blockage of the needle causing no dose and b) risk of Injection of drug containing particulates. The sponsor asserts that both risks were evaluated and that no additional risks have been identified during the risk assessment. The sponsor performed testing on pre-filled syringes as well as on devices in which the needle shield was rotated against the needle to the worst theoretical degree (65 degrees angle) in order to support the fact that such degree of rotation does not expose any risk of coring. The firm conducted testing on 250 pre-filled syringes and 60 devices, and they reported that there was no coring detected in the testing. **The response is acceptable.***

The BLA holder has provided all necessary testing. CDRH/ODE/GHDB has no further concerns regarding the device component of this combination product.

Digital Signature Concurrence Table	
Reviewer Sign-Off Keith Marin	
Branch Chief Sign-Off Richard Chapman	

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

05/19/2014

CDRH/ODE/GHDB consultative review entered into DARRTS on behalf of Keith Marin

Inter-Center Consultation Memorandum

From: Doran Fink, MD, PhD, CBER/OVRR/DVRPA
To: Amy Weitach, MD, CDER/OND/DPPP
Re: Labeling of vaccine immune responses in patients treated with Cosentyx
Through: Andrea Hulse, MD, Acting Branch Chief, CBER/OVRR/DVRPA/CRB-2
Wellington Sun, MD, Director, CBER/OVRR/DVRPA
Date: 13 May 2014

Background:

Novartis Pharmaceuticals Corporation has submitted a Biologics License Application (BLA) for Cosentyx (secukinimab), a monoclonal antibody against interleukin 17A (IL-17A), for treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The proposed usage is 300 mg injected subcutaneously on a weekly schedule for 4 weeks and then monthly thereafter. Included in the BLA submission are data from an open-label, single dose study (CAIN457A2224) to evaluate whether exposure to Cosentyx affected antibody responses elicited by meningococcal and influenza vaccines. Based on the results of this study, Novartis proposes the following language in Section 5 (Warnings and Precautions) of the package insert:



Similar to previously approved biologic immunomodulatory drugs, the proposed package insert also states that live vaccines should not be given concomitantly with Cosentyx.

The reviewing division (CDER/OND/DPPP) seeks advice from CBER/OVRR/DVRPA as to whether the submitted study supports the applicant's proposed labeling, noting that the labels for previously approved biologic immunomodulatory drugs have included a general warning that non-live vaccinations received concomitantly with these drugs may not elicit an immune response sufficient to prevent disease. DPPP also notes that the package insert for Simponi (golimumab), a monoclonal antibody against tumor necrosis factor alpha approved for treatment of several autoimmune diseases, contains the following language in Section 5 (Warnings and Precautions), which is similar to the language proposed by Novartis for Cosentyx:

In the Phase 3 PsA trial, after pneumococcal vaccination, a similar proportion of SIMPONI-treated and placebo-treated patients were able to mount an adequate immune response of at least a 2-fold increase in antibody titers to pneumococcal polysaccharide vaccine. In both SIMPONI-treated and placebo-treated patients, the proportions of patients with response to pneumococcal vaccine were lower among patients receiving MTX compared with patients not receiving MTX. The data suggest that SIMPONI does not suppress the humoral immune response to the pneumococcal vaccine.

Discussion of Study CAIN457A2224:

This was an open-label study to evaluate the effect of a single 150 mg dose of secukinimab on antibody responses to meningococcal and influenza vaccinations. The study was conducted in France between 14 January 2011 and 20 April 2011. Fifty healthy male and female subjects 18-55 years of age were randomized 1:1 to receive either a single dose of secukinimab 150 mg or no treatment on Day 1. All subjects were then vaccinated 14 days later with Aggripal (2010-2011 trivalent inactivated seasonal influenza vaccine from strains A/H1N1/California, A/H3N2/Perth, and B/Brisbane) and Menjugate (group C meningococcal conjugate vaccine from strain C11). Both vaccines were manufactured by Novartis, approved for use in the EU, and sourced from local pharmacies. Eligibility criteria excluded any subject who received vaccination of any kind within the previous year, meningococcal vaccination at any time, or influenza vaccination within the previous two years.

Humoral immune responses were assessed at baseline (on the day of vaccination) and then at one, two, four, and six weeks post-vaccination. Responses to influenza vaccination were assessed by hemagglutinin inhibition (HI) assay for each vaccine strain and were analyzed by percent of subjects with titer $\geq 1:40$ and percent of subjects with ≥ 4 -fold increase in reciprocal titer from baseline for at least two of the three vaccine strains (seroresponse rate). Responses to meningococcal vaccine were assessed by serum bactericidal assay (SBA) and were analyzed by percent of subjects with titer $\geq 1:8$ and percent of subjects with ≥ 4 -fold increase in reciprocal titer from baseline (seroresponse rate). The study report states that the HI and SBA assays were performed using validated methods (HI and SBA assays performed at Novartis central laboratories have been validated to support licensure of their Agriflu trivalent inactivated seasonal influenza vaccine and Menveo quadrivalent meningococcal conjugate vaccine). HI titers $< 1:10$ were imputed to 1:5, while SBA titers $< 1:4$ were imputed to 1:2.

All 50 subjects completed the study, and there were no differences in baseline demographic parameters. Only a few subjects had missing serology data: one subject had missing Visit 3 (day of vaccination) HI titers for Perth and Brisbane strains, so the titers from Visit 2 (day of secukinimab injection) were carried forward as the baseline for this subject; and another subject had a missing SBA titer at Visit 7 (end of study).

Influenza vaccine antibody responses

The proportions of subjects with baseline HI titers $\geq 1:40$ for each strain were as follows: Brisbane – 3/25 (12%) for both the treatment and control groups; Perth – 6/25 (24%) for the treatment group vs. 14/25 (56%) for the control group; and California – 6/25 (24%) for the treatment group vs. 8/25 (32%) for the control group. Seroresponse to influenza vaccine at four weeks post-vaccination occurred in 20/25 (80%) of subjects in the treatment group compared to 20/25 (80%) of subjects in the control group (difference of 0; 95% CI [-0.22, 0.22]).

Seroresponse rates were similar for both treatment and control groups at two and six weeks post-vaccination compared to the primary analysis time point (and compared between treatment groups), though at one week post-vaccination seroresponse rates were 1/25 (4%) for the treatment group vs. 8/25 (32%) for the control group. Strain-specific seroresponse rates at four weeks post-vaccination were similar between strains and between treatment groups (68-80%).

The proportions of subjects with HI titers $\geq 1:40$ at four weeks post-vaccination were as follows: Brisbane - 23/25 (92%) in the treatment group vs. 25/25 (100%) in the control group; Perth - 25/25 (100%) in the treatment group vs. 24/25 (96%) in the control group; and California - 22/25 (88%) in the treatment group vs. 22/25 (88%) in the control group. HI geometric mean titers (GMTs) and mean fold-rise from baseline for California and Brisbane strains were generally 1.5-fold to 2-fold higher in the control group compared to the treatment group at all post-vaccination time points, though with overlapping 90% CI, while GMTs and mean fold-rise from baseline for Perth strain were similar between treatment groups. Although not presented in the study report, the strain-specific GMT ratios (control group over treatment group) at four weeks-post vaccination calculated by this reviewer are as follows: California – 1.6 (95% CI [0.5, 4.9]); Perth – 1.5 (95% CI [0.7, 3.3]); and Brisbane – 1.6 (95% CI [0.8, 3.1]).

Meningococcal vaccine antibody responses

The proportions of subjects with baseline SBA titers $\geq 1:8$ were 10/25 (40%) in the treatment group vs. 12/25 (48%) in the control group. Seroreponse to meningococcal vaccine occurred at four weeks post-vaccination in 19/25 (76%) of subjects in the treatment group compared to 18/25 (72%) of subjects in the control group (difference of -4%; 95% CI [-27%, 19%]). Seroreponse rates were similar for both treatment and control groups at two and six weeks post-vaccination compared to the primary analysis time point (and compared between treatment groups), though at one week post-vaccination, seroreponse rates were 8/25 (32%) for the treatment group vs. 10/25 (40%) for the control group.

The proportions of subjects with SBA titers $\geq 1:8$ at four weeks post-vaccination were 25/25 (100%) in the treatment group vs. 23/25 (92%) in the control group. SBA GMTs and mean fold-rise from baseline were similar between treatment groups at all post-vaccination time points except one week post-vaccination, where the control group had a 2-fold higher GMT and 1.3-fold higher mean fold-rise from baseline compared to the treatment group (though with overlapping 90% CI), and at six weeks post-vaccination, where the control group had a 1.6-fold higher GMT compared to the treatment group (though with overlapping 90% CI). Although not presented in the study report, the GMT ratio (control group over treatment group) at four weeks-post vaccination calculated by this reviewer is 1.3 (95% CI [0.5, 3.4]).

Interpretation of antibody response data

The submitted study presents non-inferiority comparisons of antibody responses to influenza and meningococcal vaccines in secukinimab-treated vs. untreated subjects. The point estimates for influenza vaccine seroreponse rates at four weeks post-vaccination appear to be similar between control and treatment groups, but due to the small sample size the 95% CI excludes a difference no smaller than 22%. The point estimates for meningococcal vaccine seroreponse rates at four weeks post-vaccination also appear to be similar between treatment groups, but the 95% CI excludes a difference no smaller than 19%. Similarly, the 95% CI for strain-specific influenza GMT ratios at four weeks post-vaccination exclude differences no smaller than 3.1-fold to 4.9-fold between control and treatment groups, while the 95% CI for meningococcal GMT ratio at four weeks post-vaccination excludes a difference no smaller than 3.4-fold.

In regulatory practice, this type of immunobridging study may support extension of an approved indication for a licensed vaccine to a population in which a comparative clinical endpoint efficacy study is challenging (for example, see the FDA Guidance for Industry: Clinical Data Needed to Support the Licensure of Seasonal Inactivated Influenza Vaccines¹). Although variations may arise on a case by case basis, CBER standards for a successful immunobridging study generally require that the upper limit of the 95% CI for ratio of post-vaccination GMTs (approved population over new population) excludes a ratio higher than 1.5 and that the upper bound of the 95% CI for difference in seroresponse rates (approved population minus new population) excludes a difference greater than 10%. Furthermore, the overall seroresponse definition used in this study for influenza vaccine is less rigorous than the typical requirements for seasonal influenza vaccine immunobridging studies, where responses to each strain are compared independently and must all be non-inferior. Thus, the data from this study would not meet CBER's regulatory standards for an immunobridging demonstration of vaccine effectiveness in patients treated with secukinimab.

Another important consideration is that the secukinimab treatment administered in this study (a single dose of 150 mg two weeks prior to vaccination) may not affect vaccine immune responses as profoundly as the intended long-term treatment regimen of 300 mg weekly for four weeks followed by 300 mg monthly. The potential for a more profound effect is concerning given the trend toward decreased HI GMTs at all post-vaccination time points and decreased SBA GMT at the six week post-vaccination time point in the treated group compared to the control group. Consequently, we do not concur with the proposed statement in the Cosentyx package insert that “
[REDACTED] (b) (4)
.”

Even if the data had met the regulatory standard, a key consideration for immunobridging studies is that the measured immune parameter does not assess all components of the immune response involved in conferring protection against disease. The thresholds of $\geq 1:40$ for HI titer and $\geq 1:8$ for SBA titer are accepted for regulatory purposes as clinically meaningful functional measures of humoral immune responses in healthy individuals but are not established mechanistic correlates of protection. Consequently, the assumption that a non-inferior antibody response translates to non-inferior protection must be predicated in large part on an assumption that the immune components not measured (e.g., cellular responses) will also be non-inferior. This assumption may be sound when comparing two populations that are both generally healthy but is not necessarily valid in situations where one population has compromised cellular immunity, which may affect not only initial response to the vaccine but also recall response to challenge by the relevant pathogen. The exact role of IL-17 in initial and memory vaccine responses, and the effects of its inhibition, are not well defined. Consequently, we also do not concur with the proposed assertion in the Cosentyx package insert that [REDACTED] (b) (4)

” We note the similar assertion in the approved package insert for Simponi regarding antibody responses to pneumococcal vaccine. We were not consulted regarding this language and would have disagreed with it if given the opportunity to comment.

¹<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074794.htm>

Recommendations:

For the reasons stated above, we do not concur with the proposed language in the Cosentyx package insert [REDACTED] (b) (4)

[REDACTED]. However, we acknowledge that despite not having definitive evidence of vaccine effectiveness in patients undergoing Cosentyx therapy, the benefit/risk balances are likely to remain favorable in situations where the vaccines are indicated for these patients, and healthcare practitioners may appreciate knowing about this study if described in the proper context.

We recommend that the proposed language in Section 5 regarding non-live vaccinations be revised to state, “Non-live vaccinations received during a course of COSENTYX may not elicit an immune response sufficient to prevent disease,” and that the following language may be added to Section 7 (Drug Interactions):

Healthy individuals who received a single 150 mg dose of COSENTYX two weeks prior to vaccination with a group C meningococcal polysaccharide conjugate vaccine (MENJUGATE) and an inactivated seasonal influenza vaccine (AGGRIPAL) had similar antibody responses compared to individuals who did not receive COSENTYX prior to vaccination. The clinical effectiveness of meningococcal and influenza vaccines has not been assessed in patients undergoing treatment with COSENTYX.

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/s/

MATTHEW E WHITE

05/15/2014

CBER DVRPA consultative review entered into DARRTS on behalf of Doran Fink



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDRH Human Factors Consult Review

DATE: March 6, 2014

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGRID
THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGRID
TO: Mathew White, Regulatory Project Manager, CDER/OND/ODEIII/DDDP

SUBJECT: **BLA 125504**
Applicant: Novartis Pharmaceuticals
Device Constituent: prefilled syringe and peninjector
Drug Constituent: Cosentyx
Intended Treatment: Severe plaque psoriasis
CDRH CTS Tracking No.: ICC 1300644

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Combination Product Device Information

Submission No.: BLA 125504

Applicant: Novartis Pharmaceuticals

Device Constituent: prefilled syringe and peninjector

Drug Constituent: Cosentyx

Intended Treatment: Severe plaque psoriasis

CDRH Human Factors Involvement History

- 12/2/2013 – CDRH HF was requested to review the human factors validation study report included in the BLA.
- 3/14/2014 – CDRH HF provided review recommendation. No deficiencies were identified.

Overview and Recommendation

The Division of Dermatology and Dental Products requested a consultative review from CDRH Human Factors team to review the human factors validation study reports contained in the BLA. The Sponsor submitted two human factors study reports, one for the prefilled syringe, and one for the pen.

Novartis conducted a risk analysis and formative studies prior to arriving at the finalized products that were used in the validation studies. The human factors validation study for the prefilled configuration was conducted with 138 participant's representative of the intended users. Of these, 105 participants received a realistic, pre-defined training, returning for a simulated use assessment session either one week or one month after their training; and 33 participants (including healthcare professionals) were untrained. The human factors validation study for the pen configuration was conducted with 165 participant's representative of intended users. Of these, 94 participants received realistic, predefined training and returned for a simulated use assessment session either one week or four weeks after their training; and 71 participants were untrained and carried out their simulated use assessment without support.

The study results for the prefilled syringe showed one participant who failed to administer an injection successfully. The study results for the pen showed failures associated with participants not waiting for the 2nd click to complete the injection. The failures would represent instances of underdose in actual use. The consultant and medical officer discussed these failures and it was determined that they would not be clinically significant. There were several reported confusions/difficulties in both the prefilled and pen study. Changes were made to the Instructions for Use to address the failures and difficulties. The Sponsor supplied the revised IFUs in the study reports.

The consultant finds the study results and analyses acceptable. Given the nature of the proposed IFU changes, the consultant does not believe that additional human factors validation study is needed.

CDRH Human Factors Review

The Sponsor reported to have conducted a risk analysis and formative studies prior to arriving at the finalized products that were used in the validation studies.

Human Factors Study Report for Prefilled Syringe

The human factors validation study for the prefilled configuration was conducted with 138 participants representing the intended users. Of these, 105 participants received a realistic, pre-defined training, returning for a simulated use assessment session either one week or one month after their training; and 33 participants (including healthcare professionals) were untrained.

The study results showed that 104/105 trained participants, and 33/33 untrained participants delivered their first injection successfully. The results also showed that 18/138 participants experienced some confusions while performing their injections. The following provides some descriptions of the reported confusions:

- Injection technique intentionally not as instructed leading to slight reduction in dose (e.g. checking that the medication flows/the needle is not blocked by pressing a few drops out before injection)
- Injection technique unintentionally not as instructed leading to slight reduction in dose (e.g. inadvertently pushing plunger slightly before needle inserted into skin)
- Close call (e.g. pulling on the plunger when removing the needle cap but recovering before the plunger was removed)
- Confusion regarding device operation (e.g. thinking that the needle had been left in the skin after the needle guard was deployed)
- Inability to comprehend instruction that has associated high severity harm (e.g. the meaning of a “sharps container”)
- Inadvertent removal of the plunger (including the rubber stopper) completely out of the syringe barrel

The Instructions for Use was modified to address the reported confusions above.

Pen Human Factors Study Report for the Pen Configuration

The human factors validation study for the pen configuration was conducted with 165 participants representing the intended users. Of these, 94 participants received realistic, predefined training and returned for a simulated use assessment session either one week or four weeks after their training; and 71 participants were untrained and carried out their simulated use assessment without support.

During the first unsupervised injection:

- Seven (7/94) trained participants did not complete the injection successfully due to failure to activate the (b) (4) AI, to hold the (b) (4) AI against the injection site until the 2nd ‘click’ (5 instances), and due to moderator intervention (two instances) to prevent possible needle stick injuries (identifying the correct end of the pen to perform injection)
- Six (6/71) untrained participants failed to deliver their first unsupervised injection due to failure to failed to hold the (b) (4) AI against the injection site until the 2nd ‘click’

During the one week and four week assessments, two (2/56) and five (5/38) trained participants failed to perform the injection respectively due to failure to hold the (b) (4) AI against the

injection site until the 2nd 'click.' These results were intended to demonstrate user performance after some time has elapsed between receiving training and performing the next injection.

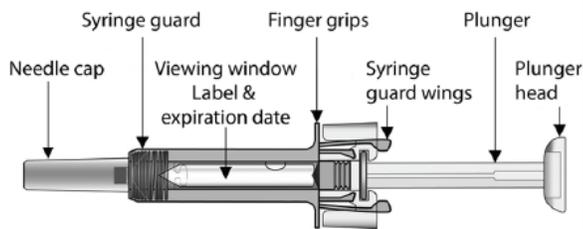
In addition, there were 20/165 participants (trained and untrained) experienced difficulty but were able to successfully complete an injection. These difficulties were due to:

- Green Plunger Confusion: Confusion over the appearance or the motion (e.g. direction or speed) of the (b) (4) AI's green plunger.
- Confusion over how to activate the injection: tried to activate the (b) (4) AI by pressing a button rather than pushing down on the device body to trigger the injection (1st 'click').
- Inadvertent 2nd 'click' removal: when the mechanism activated on the 2nd 'click', the injector 'sprang-up' out of the participant's hand as they applied insufficient grip and downward force to the injector to keep it in place. Participants therefore received a 'clinically effective' albeit 'wet' injection
- Struggle to maintain downward pressure: struggled to keep the (b) (4) AI pressed firmly against the skin until the 2nd 'click' was heard and the green plunger had stopped moving.

Several modifications to the Instructions for Use have been made to address the task failures associated with the 2nd click issue.

Appendix 1: Device Description

Secukinumab is supplied as a pre-filled syringe within a safety device known as the (b) (4). This needle guard is an anti-needlestick accessory cleared by (b) (4) and 510(k) (b) (4) in September 2012 with the following indications for use: “ (b) (4)



The (b) (4) AI is a single-use, disposable drug delivery device for subcutaneous injection. The needle-based injection system is (b) (4) and designed to administer the entire contents of the pre-filled syringe in one dose. Once an injection has been delivered, the device automatically covers the needle making it safer for handling and disposal.

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/s/

MATTHEW E WHITE

03/24/2014

CDRH Human Factors review entered into DARRTS on behalf of Quynhnhu Nguyen and Ronald Kaye.



Food and Drug Administration
Center for Devices and
Radiological Health
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: February 20, 2014
From: Jacqueline Ryan, Combination Products Team Leader, WO66, RM 1257
General Hospital Devices Branch, DAGID, ODE, CDRH
To: Amy Voitach, Medical Officer, OMPT/CDER/OND/ODEIII/DDDP
Subject: CDRH Consult, CTS ICC 1300617, BLA 125504, PFS and AI to deliver
COSENTYX™ (secukinumab)

1. Issue

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding BLA 125504. The device constituent of this combination product consists of a PFS and AI to deliver COSENTYX™ (secukinumab). This consult consists of an initial BLA filing review and initial device labeling review.

2. Device Descriptions

The primary container closure for the drug product is the (b) (4) 1.0 mL pre-filled syringe with 27G X 1/2 inch staked needle with (b) (4) (b) (4) plunger stopper. A rubber needle shield encapsulates the needle; the rigid shell stabilizes and protects the closure. The syringe barrel, needle and plunger stopper are (b) (4).

For the PFS product presentation, the container closure system also includes the (b) (4) as a safety mechanism to reduce occurrence of accidental needle sticks. (b) (4) does not contact the drug product. The device was cleared by FDA under 510(k) premarket submission (b) (4).

The (b) (4) auto-injector is a fixed single dose, disposable, (b) (4) drug delivery device developed by (b) (4). (b) (4) is designed to provide a convenient means to inject a single medication subcutaneously from a pre-filled syringe. The device consists of Front Subassembly and Rear Subassembly that are designed to enclose drug product contained in a (b) (4) 1.0 mL pre-filled syringe with 27G X 1/2 inch stake-on needle. The syringe holds the entire dose, which can be expelled as a fixed dose. The labeled volume is 1.00ml, and the

accuracy for the minimum dose is accordance to the pen-injector standard. The needle is hidden during the entire injection process

The (b) (4) consists of (b) (4) sub-assemblies specifically designed to enclose a pre-filled in a (b) (4) 1.0 mL syringe with 27GX 1/2 inch stake-on needle. While the injection is taking place, the user can hear two audible clicks: start and finish of the dose. After the injection, the Shield is automatically locked to prevent needle stick.

The AI is made up of the following parts/features (as shown in [Figure 3-1](#)):

- Cap (protects the needle before use)
- Cap Seal (tamper evidence feature)
- RNS (protects needle before use) – part of the PFS
- Needle (inserts into the skin) – part of PFS
- Needle Guard (Sharps Injury Prevention Feature - SIPF)
- Inspection Window (allows user to check the progress of the injection (green indicator) and check the appearance of the drug before use)
- Green Indicator (shows the progress of the injection as it slowly progresses through the inspection window during injection)



3. Documents Reviewed

MAF (b) (4)



Email: [REDACTED] (b) (4)

DMF [REDACTED] (b) (4)

BLA 125504

4. CDRH Review and Comments

[REDACTED] (b) (4)
[REDACTED] 1.0 mL pre-filled syringe with 27G X 1/2 inch stake-on needle was reviewed and appears to be adequate for filing.

[REDACTED] (b) (4)
[REDACTED] is included with the PFS presentation as a safety mechanism to reduce occurrence of accidental needle sticks. The device was cleared by FDA under 510(k) premarket submission [REDACTED] (b) (4)

MAF [REDACTED] (b) (4) Injector

Biocompatibility

The recommended biocompatibility testing for the [REDACTED] (b) (4), based upon its use in the combination product, is identified in ISO 10993-1 "Biological Evaluation of Medical Devices, Part 1: Evaluation and Testing". These tests include Cytotoxicity, Sensitization, and Irritation or Intracutaneous Reactivity for the biological effects of a device that is categorized as a surface device having limited contact duration (<24 h) with human skin. The plastic components of [REDACTED] (b) (4) that have direct contact with the user skin were tested by [REDACTED] (b) (4) in the US and the test reports are included in Attachment 6.

Shelf Life/Accelerated Aging

The shelf life of the [REDACTED] (b) (4) Auto-injector is based upon accelerated aging studies using the Arrhenius Reaction Rate Law. The Arrhenius Reaction Rate Law is commonly used in aging studies for polymer-based devices. Further detail of the Arrhenius Reaction Rate Law and the aging test protocol can be found in Attachment 8.

Functional Testing

[REDACTED] (b) (4) has conducted bench testing to demonstrate the functionality and reliability of [REDACTED] (b) (4) auto-injector, which includes function test, attribute test and component test

based on the design input requirements of the (b) (4) auto-injector. The function test and attribute test were performed using the final assembled (b) (4) with the pre-filled syringe. The assessment for the completion of user sequence was demonstrated by attribute test for which the (b) (4) was manually activated using an injection pad. The test summary and result are provided in Table 4 and Attachment 7.

Dose Accuracy Testing

The (b) (4) test for dose accuracy is a measurement of delivered volume and assessment of completeness-of-injection. Dose accuracy is operationally defined by (b) (4) as the expelling of the labeled volume (or greater) from the prefilled syringe. Although (b) (4) uses the term "dose accuracy" in some documents, (b) (4) does not evaluate dose accuracy, which is a function of the ability to set a dose, and for a single use injector the volume of dose expelled is dependent upon the actual fill volume of the syringe. The delivered volume tested by (b) (4) does compare the expelled volume to the labeled volume of the syringe, and there is a visual confirmation of the travel of the plunger rod that a complete forward movement of the injection plunger rod has occurred.

Packaging and Shipping

One cardboard shipping box containing each of Front or Rear subassemblies were tested to simulate a general distribution cycle including manual handling, stacked vibration, vehicle vibration, concentrated impact and manual handling per ASTM D4 J69-09 Standard Practice for Performance Testing of Shipping Containers and Systems.

Labeling and IFU for PFS and Auto Injector

Regarding instructions for use, CDRH Device Evaluation requests that the instructions for use are validated by Human Factors Usability Testing prior to final ODE review.

5. CDRH ODE Device Evaluation Recommendations

CDRH ODE is asking CDER ONDQA to send a request for additional information to the authorized representative for MAF (b) (4). Otherwise the data presented appears to be adequate to file the BLA from a device standpoint.

Regarding instructions for use, CDRH Device Evaluation requests that the instructions for use are validated by Human Factors Usability Testing prior to final ODE review. A consult to CDRH ODE Human Factors Team should be sent to review completed Human Factors validation studies or a proposed Human Factors protocol once the final product presentation has been established and no further device changes will be made. CDRH ODE has reviewed the proposed packaging and has no concerns regarding the adequacy of package labeling.

A separate consult should be sent to CDRH Office of Compliance regarding the possible need for a facilities inspection.

As stated above, initial review indicates that the device performance data submitted are adequate for filing. However, the following request for additional information should be sent to the MAF holder for the (b) (4) injector. MAF requests for additional information are sent through CDER ONDQA.

MAF (b) (4)
(b) (4)

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.

Digital Signature Concurrence Table	
Reviewer Sign-Off Jacqueline Ryan	
Branch Chief Sign-Off Richard Chapman	

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/s/

MATTHEW E WHITE

03/13/2014

CDRH Filing Review entered into DARRTS on behalf of Jacqueline Ryan and Richard Chapman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing Quality

DATE: January 6, 2014
TO: Amy Voitach, CDER - ODE III/DDDP
Amy.Voitach@fda.hhs.gov
Cc: Office of combination products at combination@fda.gov
Through: Carl Fischer, PhD, Chief, General Hospital Devices Branch,
Division of Manufacturing Quality, Office of Compliance, CDRH,
WO-66, Room 3526

For Carl Fischer

From: Viky Verna, MS BME, MS Pharm, Respiratory ENT General
Hospital and Ophthalmology Devices Branch, Division of
Manufacturing Quality, Office of Compliance, CDRH, WO66,
Room 2628

Firm: Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, New Jersey 07936-1080

Application # Original BLA 125504

Product Name: Cosentyx (secukinumab)

Consult Instructions: Novartis Pharmaceuticals submitted the NME BLA 125504
Cosentyx, powder for solution, solution for injection, 150 mg, 150
mg/mL. The proposed labeling includes 3 different presentations:
Single use Sensoready pens, Single use pre-filled syringe and
Single use vials. DDDP requests determination as to whether a
device related inspection is required. The TB-EER with
manufacturing site information is attached.

Background

On November 27, 2013, the Office of Compliance at CDRH received a consult request from Amy Voitach, CDER Reviewer, to evaluate the appropriate materials submitted by

the applicant, Novartis Pharmaceuticals Corporation, for the Cosentyx combination product.

Combination Product Description

The COSENTYX™ (secukinumab) product is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Secukinumab is also known as AIN457.

The firm is proposing to supply the product as 150 mg secukinumab in 1 mL of sterile solution for injection in a single-use prefilled SensoReady® pen and a single-use prefilled syringe (PFS) for self/home administration, and as 150 mg secukinumab as a powder for solution for injection in a single-use glass vial for administration by a health care professional.



The autoinjector integrates AIN457 in PFS and includes (figure 1):

- Cap
- Body containing the injector mechanism and syringe carrier
- Inspection window
- Green indicator

DOCUMENT REVIEW

The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

In the submission, the firm gave a description of each of the components and described the different assembly processes. The container closure system for AIN457 150 mg/1mL Solution for injection in pre-filled autoinjector (AI) consists of a sterile, single use Pre-Filled Syringe (PFS) as the primary packaging component of the drug product (i.e., (b) (4)) and an autoinjector/pen ((b) (4) -02); a device constituent that is used in combination with the PFS for drug delivery.

When it is intended to be marketed as a single use (PFS), the AIN457 150 mg/1mL Solution for injection in pre-filled syringe it is packaged as a pre-filled 1 mL long glass syringe with (b) (4) plunger stopper, staked needle 27G ½” and rigid needle shield which are supplied by (b) (4) .

The PFS can then undergo further assembly into the AI, a drug-device combination product designed to administer the entire content of the AIN457 150 mg/1mL Solution for injection in pre-filled syringe in one dose.

The firm provided a copy of the MAF letter of authorization for the (b) (4) autoinjector from the autoinjector component supplier, (b) (4) . The PFS is assembled into the autoinjector by Novartis.

The firm explained that its Supplier Quality program ensures the supplier maintains a quality control program for the primary packaging components, as well as secondary packaging components. For primary packaging components, Novartis accepts a packaging component lot from a supplier based on receipt of their Certificate of Analysis (CoA) and the internal performance of an identification test, which also generates an internal CoA.

Novartis’ Supplier Quality program ensures the supplier maintains a quality control program for the supplied components. Novartis performs incoming inspection to ensure specifications for the supplied components are met. It reviews supplier Certificates of Analyses (COAs) and/or Certificates of Compliance (CoCs), as well as testing and generating internal CoAs to signify acceptance and release of the supplied components.

Per the firm’s documents, the assembly process of AIN457 150 mg/1mL Solution for injection in pre-filled autoinjector has been validated using three commercial scale production batches which have been processed in the same manufacturing facilities, using the same assembly process (figure 2) and the same equipment as for the batches intended for marketing.

All three batches fully met the pre-determined acceptance criteria. Therefore the firm believes it has been demonstrated that the assembly process is robust and consistently yields an assembled product capable of meeting the pre-defined quality characteristics.

Deficiencies:

The following deficiencies were noted during the review:

1. The Applicant described and provided summarized results of the validation activities. However the firm did not provide its design control procedure covering the Design Input, Design output and Design Validation/Verification, including design changes, for the overall finished combination product in order to ensure that specified design requirements are met. Therefore, the information provided by the firm has inadequately addressed the requirements of 21 CFR 820.30.
2. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.

Deficiencies to be conveyed to the applicant

Novartis Pharmaceuticals Corporation

One Health Plaza
East Hanover, New Jersey 07936-1080

The following deficiencies have been identified while doing the desk review of application original BLA 125504, in reference to applicable 21 CFR 820 regulations and the manufacturing of the finished combination product:

1. The information provided by your firm has inadequately addressed the requirements of 21 CFR 820.30. In the submission, you provided information on the design validation activities. However your firm did not provide its design control procedure covering the Design Input, Design output and Design Validation/Verification, including design changes, for the overall finished combination product in order to ensure that specified design requirements are met.
2. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.

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>

REGULATORY HISTORY

After reviewing the application, the following facilities were identified as being subject to applicable Medical Device Regulations under 21 CFR part 820:

1. Novartis Pharma Stein AG
Schaffhauserstrasse 101
Stein, Switzerland
FEI: 3002653483

An analysis of the firm's inspection history over the past 2 years showed that a drug inspection conducted on June 2012, while revealing some deficiencies, was classified NAI.

2.



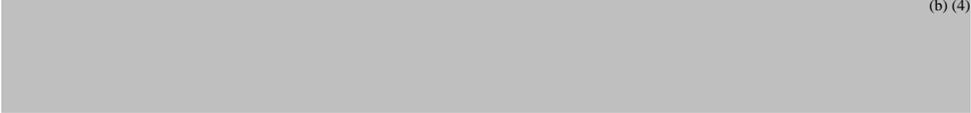
An analysis of the firm's inspection history over the past 2 years showed that a drug inspection conducted on [REDACTED] (b) (4), revealed no deficiencies and was classified NAI.

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of the Original BLA 125504.

Application BLA 125504 approvability under the Medical Device Regulations should be delayed until the sponsor provides the additional information requested and an adequate desk review of the application has been completed; and the inspection of the following site has been conducted and deemed acceptable:

- Novartis Pharma Stein AG, Schaffhauserstrasse 101, Stein, Switzerland
FEI: 3002653483

-  (b) (4)

Viky G. D. Verna, MS BME, MS Pharm

Prepared: VVerna: January 6, 2014
Revised: MITejero: January 8, 2014
Revised: Vverna:

cc:

WO66-2628 Viky Verna
WO66-2628 Carl Fischer
WO66-3554 Isabel Tejero
WO22-5180 Amy Weitach
combination@fda.gov (OCP)

BLA 125504
CTS: ICC1300619

Inspectional guidance

CDRH recommends the inspection under the applicable Medical Device Regulations of:

- Novartis Pharma Stein AG, Schaffhauserstrasse 101, Stein, Switzerland
FEI: 3002653483

-  (b) (4)

A comprehensive baseline Level 2 inspection is recommended focusing on Management Responsibility (21 CFR 820.20), Purchasing Controls (21 CFR 820.50), CAPA (21 CFR 820.100), and Design Controls (21 CFR 820.30)

Additionally, evaluate the manufacturing activities associated final acceptance activities.

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

01/09/2014

CDRH, OC, Division of Manufacturing Quality Review. Entered into DARRTS on behalf of Vicky Verna and Dr. Carl Fischer.

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
BLA# 125504	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Cosentyx Established/Proper Name: Secukinumab Dosage Form: Powder for solution, solution for injection Strengths: 150 mg, 150 mg/mL		
Applicant: Novartis Pharmaceuticals Corporation Agent for Applicant (if applicable):		
Date of Application: October 22, 2013 Date of Receipt: October 24, 2013 Date clock started after UN:		
PDUFA Goal Date: October 24, 2014		Action Goal Date (if different):
Filing Date: December 23, 2013		Date of Filing Meeting: December 6, 2013
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed indication(s)/Proposed change(s): Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input checked="" type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 100418				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Standard 12 Month/ The Program
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

User Fee Status <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i>					
Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Does not contain evidence that the deferred studies are being conducted or will be conducted with due diligence and at the earliest time possible.
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input checked="" type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Other Consults	YES	NO	NA	Comment

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	IFU consulted to CDRH. Device inspection to CDRH OC HFE Study reports to CDRH
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 24, 2013 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 6, 2013

BLA #: 125504

PROPRIETARY NAME: Cosentyx

ESTABLISHED/PROPER NAME: Secukinumab

DOSAGE FORM/STRENGTH: Powder for solution, solution for injection, 150 mg, 150 mg/mL

APPLICANT: Novartis Pharmaceuticals Corporation

PROPOSED INDICATION: Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

BACKGROUND: New NME BLA received October 22, 2013. To be reviewed under “The Program”

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Matthew White	Y
	CPMS/TL:	Barbara Gould	Y
Cross-Discipline Team Leader (CDTL)	David Kettl		
Clinical	Reviewer:	Amy Voitach	Y
	TL:	David Kettl	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jie Wang	Y
	TL:	Yow-Ming Wang	Y
Biostatistics	Reviewer:	Carin Kim	Y
	TL:	Mohamed Alesh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Jill Merrill	N
	TL:	Barbara Hill	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Tura Camilli	Y
	TL:	Sarah Kennett	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Reyes Candau-Chacon (drug substance), Kalavati Suvarna (drug product)	N
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Lubna Merchant	Y
OSE/DRISK (REMS)	Reviewer:	Carolyn Yancey	Y
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Pharmacometrics: Jiang Liu, Yaning Wang CDRH ODE: Jacqueline Ryan/Richard Chapman CDRH OC: Viky Verna/Carl Fischer CDRH Human Factors: QuynhNhu Nguyen PLT: Sharon Mills/Barbara Fuller		
Other attendees	Dr. Julie Beitz, Director, ODE III Dr. Susan J. Walke, Director, DDDP Dr. Stanka Kukich, Deputy Director, DDDP Dr. Tatiana Oussova, Deputy Director for Safety, DDDP		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments: No comments</p>	<input type="checkbox"/> Not Applicable

<p>CLINICAL</p> <p>Comments: Refer to clinical filing review for information requests to be forwarded to the applicant.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments:</p> <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: Refer to biostatistics filing review for information requests to be forwarded to the applicant.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Refer to OBP filing review for information requests to be forwarded to the applicant.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p>	<input type="checkbox"/> Not Applicable

<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments: Refer to Product Quality (Biotechnology) filing review for information requests to be forwarded to the applicant.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Dr. Julie Beitz

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 3/24/14

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><u>Pediatric Plan:</u> Deferral Request: 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).</p> <p><u>Labeling:</u> In the Highlights of Prescribing Information, there is white space between the product title and the Initial U.S. Approval.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p>

<input type="checkbox"/>	Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input checked="" type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

BARBARA J GOULD
12/12/2013

**REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 0125504

Application Type: New BLA

Name of Drug/Dosage Form: Cosentyx (secukinumab) powder for solution, solution for injection, 150 mg, 150 mg/mL

Applicant: Novartis Pharmaceuticals Corporation

Receipt Date: October 24, 2013

Goal Date: October 24, 2014

1. Regulatory History and Applicant's Main Proposals

New NME BLA for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in filing letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by January 10, 2014. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT and HORIZONTAL LINES IN THE PI

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (e.g., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is one-half page or less, then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period:**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of-Cycle Period:**

- Select “YES” in the drop down menu if a waiver has been previously (or will be) granted by the review division in the approval letter and document that waiver was (or will be) granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between

Selected Requirements of Prescribing Information

the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space between the product title and the Initial U.S. Approval*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Selected Requirements of Prescribing Information

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *New NME BLA. Initial U.S. Approval date not established.*

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

YES

Selected Requirements of Prescribing Information

19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for:

- [text]
- [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

- [text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

- 1.1 [text]
- 1.2 [text]

2 DOSAGE AND ADMINISTRATION

- 2.1 [text]
- 2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 [text]
- 5.2 [text]

6 ADVERSE REACTIONS

- 6.1 [text]
- 6.2 [text]

7 DRUG INTERACTIONS

- 7.1 [text]
- 7.2 [text]

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Labor and Delivery
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 [text]
- 14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

MATTHEW E WHITE
12/10/2013