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RESEARCH**

APPLICATION NUMBER:

125521Orig1s000

OTHER REVIEW(S)

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.

NDA/BLA # BLA 125521

Product Name: Ixekizumab

PMR/PMC Description: Conduct a dose-ranging Pharmacokinetics (PK), Safety and Efficacy Study in pediatric subjects 6 to <18 years of age with moderate to severe psoriasis (with a duration of exposure to ixekizumab of at least one year).

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>03/2017</u>
	Study/Trial Completion:	<u>09/2021</u>
	Final Report Submission:	<u>03/2022</u>
	Other:	<u>N/A</u>

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-adult trials completed-ready for approval

Adult trials completed and ready for approval. Dose-ranging pharmacokinetics and safety study in pediatric subjects 6 to <18 years of age with moderate to severe psoriasis is needed to select the correct doses for evaluation in the safety and activity study in the pediatric population and to support extrapolation of efficacy. Safety and Activity Study in pediatric subjects 6 to <18 years of age with moderate to severe psoriasis is needed to establish safety in this population. Activity to be measured to support extrapolation of efficacy.

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.”

Correct doses need to be established for the pediatric population. Incorrect dosing could result in overdosing pediatric patients and this would likely be associated with increased adverse events. Safety and Activity Study in pediatric subjects 6 to 18 years of age with moderate to severe psoriasis is needed to establish safety in this population.

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.

Dose-ranging pharmacokinetics and safety study in pediatric subjects ages 6 to <18 years of age with moderate to severe psoriasis, with a study duration long enough to provide benefit. Safety and Activity Study in pediatric subjects 6 to 18 years of age with moderate to severe psoriasis, with duration of exposure to ixekizumab of at least one year.

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.

(signature line for BLAs)

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.

NDA/BLA # BLA 125521
Product Name: Ixekizumab

PMR/PMC Description: Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to ixekizumab and a non-ixekizumab systemic medication exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with psoriasis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2016</u>
	Study/Trial Completion:	<u>12/2021</u>
	Final Report Submission:	<u>06/2022</u>
	Other:	<u>N/A</u>

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

Adult trials are completed and ready for approval. Pregnant women were excluded from these previous trials and some data in this population is needed.

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.”

Moderate to severe psoriasis occurs in women of child bearing age. Therefore we expect there will be some exposure of pregnant women. Data on use of Ixekizumab in pregnant women is needed.

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.

A retrospective cohort study using claims or electronic medical record data or a case control study

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.

(signature line for BLAs)

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.

NDA/BLA # BLA 125521

Product Name: _____

PMR/PMC Description: Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to ixekizumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2017</u>
	Study/Trial Completion:	<u>05/2029</u>
	Final Report Submission:	<u>05/2030</u>
	Other:	<u>N/A</u>

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

Adult trials completed and ready for approval. Pregnant women were excluded from these trials and data in this population is needed.

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.”

Moderate to severe psoriasis occurs in women of child bearing age. Therefore we expect there will be some exposure of pregnant women. Data on use of Ixekizumab in pregnant women is needed.

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.

A prospective, registry based observational exposure cohort study in pregnant women and neonates.

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.*

(signature line for BLAs)

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.

NDA/BLA # BLA 125521
Product Name: Ixekizumab

PMR/PMC Description: Conduct a prospective, observational study to assess the long-term safety of ixekizumab 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 the course of actual clinical care. The study's primary outcome is malignancy. Secondary outcomes include, but are not limited to, serious infection, tuberculosis, opportunistic infections, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events. Describe and justify the choice of appropriate comparator population(s) for the primary objective. 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(s), with a pre-specified statistical analysis method. Specify concise case definitions and validation algorithms for both primary and secondary outcomes. For the ixekizumab-exposed and comparator(s), clearly define the study drug initiation period and any exclusion and inclusion criteria. Enroll patients over an initial 4-year period and follow for a minimum of 8 years from the time of enrollment.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2017</u>
	Study/Trial Completion:	<u>05/2029</u>
	Final Report Submission:	<u>05/2030</u>
	Other:	<u>N/A</u>

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

Ixekizumab's safety profile has been adequately assessed in the pre-approval program. However, the recommended PMR is to evaluate the occurrence of long-latency safety outcomes, including malignancy that cannot be adequately assessed in the clinical trial program. A PMR study would also allow for the evaluation of safety events which occur infrequently, such as serious infections.

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 concern that this new biologic product may increase the risk of malignancies and serious infection due to its immunosuppressive effect.

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 prospective observational study 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)
-
- 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.

(signature line for BLAs)

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.

NDA/BLA # 125521
Product Name: Ixekizumab

PMR/PMC Description: PMC: Conduct a clinical study to assess whether ixekizumab alters the metabolism or pharmacokinetics of CYP substrates in psoriasis patients treated with ixekizumab.

PMR/PMC Schedule Milestones: Final Protocol Submission: 08/2016
Study/Trial Completion: 01/2018
Final Report Submission: 05/2018
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 ixekizumab have been demonstrated in psoriasis patients. The potential drug-drug interaction between ixekizumab and CYP substrates may have impact on the PK and effective use of concomitant CYP substrates, not the safe or effective use of ixekizumab 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 ixekizumab 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 recommended 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 ixekizumab 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 ixekizumab 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 studies to evaluate whether ixekizumab alters the PK or metabolism of CYP substrates in psoriasis patients treated with ixekizumab.

(The recommended DDI study is not to address the safe or effective use of ixekizumab but to evaluate the potential impact of ixekizumab treatment on the PK of the concomitant small molecule CYP substrate drugs which psoriasis patients take.)

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/

J P PHILLIPS
03/22/2016

TATIANA OUSSOVA
03/22/2016



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs – ODE IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

M E M O R A N D U M

From: Donna Snyder, MD,
Acting Pediatric Team Leader
Division of Pediatric and Maternal Health (DPMH)

Through: John Alexander, MD, MPH,
Acting Deputy Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Dermatology and Dental Products
(DDDP)

Drug: Ixekizumab (TALTZ) 80 mg/mL prefilled syringe
or autoinjector

BLA: 125521
IND: 100834

Applicant: Eli Lilly and Company

Indication: Plaque Psoriasis

Subject: Review of Pediatric Review Committee (PeRC)
Paperwork

Materials Reviewed:

- Agreed initial Pediatric Study Plan included in the BLA submission on March 23, 2015

- DDDP letter to the sponsor confirming agreement with the iPSP, dated March 10, 2014, DARRTS Reference ID: 3467648
- DPMH consult request dated November 5, 2015, DARRTS Reference ID: 3843074

NON-RESPONSIVE

- BLA 125521 Late Cycle Meeting Minutes, dated December 11, 2015, DARRTS Reference ID: 3859021
- Sponsors response to the request to accelerate the timeline for pediatric patients, submitted to the BLA on December 21, 2015

NON-RESPONSIVE

- PeRC paperwork

Background:

DPMH was consulted to review the PeRC paperwork for ixekizumab [(TALTZ) 80 mg/mL prefilled syringe or autoinjector] submitted for the treatment of adults with moderate to severe plaque psoriasis. Ixekizumab is a humanized immunoglobulin G4 (IgG4) monoclonal antibody with activity against interleukin (IL)-17. The sponsor submitted an agreed Pediatric Study Plan (PSP) on February 14, 2014. The agreed PSP was also submitted with the application. The details are below:

Pediatric Plan Summary

The applicant requested a partial waiver for pediatric patients less than 6 years of age on the basis that treatment with ixekizumab would not offer a meaningful therapeutic benefit for this age group compared with existing therapies, and is unlikely to be used in this age group. The applicant submitted claims and prescription information (b) (4) (b) (4) to support their assertion. Of the 8992 pediatric patients under 6 years of age identified with psoriasis in the database, 48 (0.53%) had one prescription for methotrexate and only 33 (0.37%) had a prescription for a tumor necrosis factor-alpha (TNF- α) antagonist. The applicant stated that the prevalence and prescription use data support the proposed waiver in this age range.

Reviewer comment: The sponsor did not supply adequate information to support their rationale for a waiver on the grounds that ixekizumab would not offer a meaningful therapeutic benefit for this age group compared with existing therapies and is unlikely to be used. There are currently no approved existing systemic therapies for psoriasis in this age group. However, DPPP has typically issued a waiver for pediatric patients 6 years of age and younger on the grounds that studies are impossible or highly impracticable because of the low prevalence of the disease and because live vaccines are typically given in this age group, limiting the treatment of this pediatric population with a biologic

agent. The applicant has supplied the needed prevalence information to support the Division's usual grounds for a waiver.

The applicant requested a deferral of pediatric studies on the grounds that the pediatric studies had not been completed and the product is ready for approval in adults. The pediatric study plan does not include specific studies because the sponsor planned on collecting long-term safety data on the product before proposing pediatric studies. The proposed due date agreed for submitting the pediatric plan is December 1, 2022.

Reviewer comment: Because of concerns of malignancies reported in adult and pediatric patients receiving biologic products, specifically TNF- α inhibitor therapies, DDDP has, to date, either waived the requirement to do studies (i.e. adalimumab, infliximab), or instituted PREA PMRs with long timelines to allow for the collection of additional safety information in adults and from pediatric patients exposed in utero or postnatally (through breastfeeding) before studies will be required in children (i.e. ustekinumab).

At the late cycle meeting in December 2015, the Division informed the sponsor that the thinking had evolved on the timing of pediatric studies for systemic agents for the treatment of moderate to severe psoriasis. The Division noted that the IL-17 inhibitor agents have a more favorable risk/benefit profile than TNF- α inhibitor therapies. The Division had requested that the sponsor submit a plan for studies with an accelerated timeline compared to what was agreed to in the iPSP.

Subsequently, the sponsor submitted a revised pediatric plan in December 2015, to align the US program with the European Medicines Association (EMA) pediatric investigational plan (PIP). The sponsor proposed a single double-blind, randomized study to evaluate the safety, efficacy, and pharmacokinetics (PK) of ixekizumab compared to placebo in pediatric patients from 6 to less than 18 years of age who have moderate-to-severe plaque psoriasis. The sponsor plans to incorporate PK assessments into the study, with a subgroup receiving more intensive PK sampling. The timeline for completion of studies was moved up to 2021.

Evolving Pediatric Drug Development and Extrapolation for Psoriasis

Extrapolation of efficacy may potentially be allowed from adequate and well controlled-studies in adults if the pathophysiology of the disease is similar in adults and pediatric patients and the effects of the drug are similar. The Division must agree that the adult data supports a finding of efficacy in adults, and that there is adequate scientific rationale to support extrapolation. However, safety and dosing cannot be extrapolated, so studies in pediatric patients must be performed to support safety and dosing. Previously DDDP had followed a partial extrapolation paradigm, requiring one adequate and well-controlled trial in pediatric patients with psoriasis with supporting efficacy data from adult studies. Since finalizing the iPSP for ixekizumab, DDDP has had determined that full extrapolation may be appropriate for pediatric psoriasis once pharmacokinetic data based on age and/or weight are collected for pediatric subjects. An uncontrolled open-label trial in pediatric subjects to collect safety and tolerability data may be acceptable once doses matching adult exposures are identified. DDDP proposed a similar pediatric

plan for secukinumab (COSENTYX), another IL-17 inhibitor approved in January 2015 for treatment of adults with moderate to severe plaque psoriasis at a Type C meeting in September 2015.

DDDP has proposed the following studies for inclusion in the approval letter for ixekizumab based on a full extrapolation approach. A partial waiver for pediatric patients under 6 year of age will be granted for the reasons discussed above:

- A PK/dose-ranging study in subjects ages 6 to <17 years with at least 8 weeks duration
 - The purpose of the study is to determines a dose in the pediatric population that provides a drug exposure similar to that in adults
- An open-label safety and activity study in pediatric patients 7 to <17 years with duration of at least one year

The sponsor has the option of imbedding the PK study within the larger safety and efficacy study or performing two separate studies.

DDDP proposes that the initial protocol be submitted within the second quarter of 2016 and that studies be completed by the first quarter of 2021. The Division has not yet discussed the proposed studies or timeline with the applicant but plans to discuss the plan with the Pediatric Review Committee (PeRC) prior to discussing with the applicant.

DPMH Recommendations and Conclusions

DPMH met with the Division on November 10, 2015 to discuss the pediatric development program for moderate to severe psoriasis and to discuss the preparation of the PeRC documents. DPMH recommended that the PeRC documents reflect the Division's change in thinking regarding extrapolation, and the recommendation for an open-label study and acceleration on the study timelines. DPMH agrees that this plan is acceptable.

DDDP met with the PeRC on January 27, 2016 to discuss the pediatric program and the revised pediatric plan based on the ability to fully extrapolate efficacy. The PeRC agreed with the Division's plan for a partial waiver and studies as proposed by DDDP above. The PeRC recommended that the Division engage in discussions with the EMA to discuss the possibility of a unified plan for pediatric studies. See the PeRC meeting minutes for a detailed discussion of the issues.

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/s/

DONNA L SNYDER
02/19/2016

JOHN J ALEXANDER
02/19/2016



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

FINAL LABEL AND LABELING REVIEW

Date:	February 8, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad -S <small>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: 2016.02.08 16:11:25 -0500</small>
Through:	Michael Xu Di, PhD, Product Quality Reviewer Division of Biotechnology Research and Review III Xu Di -S <small>Digitally signed by Xu Di -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xu Di -S, 0.9.2342.19200300.100.1.1=2000501033 Date: 2016.02.08 16:43:27 -0500</small>
Application:	BLA 125521/0
Product:	Taltz (ixekizumab)
Applicant:	Eli Lilly and Company
Submission Dates:	March 23; December 14 2015; February 3 2016

Executive Summary:

The container labels and carton labeling for Taltz (ixekizumab) 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 (USP), USP 38/NF 33 [December 1, 2015 to April 30, 2016]. Labeling deficiencies were identified and resolved. The prefilled autoinjector (AI) container label submitted on December 14, 2015; and the prefilled syringe (PFS) container label and carton labeling (AI and PFS) submitted on February 3, 2016 are acceptable.

Background and Summary Description:

The Applicant submitted BLA 125521 Taltz™ (ixekizumab) on March 23 2015. Table 1 lists the proposed characteristics of Taltz™ (ixekizumab).

Table 1: Proposed Product Characteristics of Taltz™ (ixekizumab).

Proprietary Name:	Taltz
Proper Name:	ixekizumab
Indication:	interleukin-17A antagonist indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Dose:	160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80 mg injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.
Route of Administration:	Subcutaneous
Dosage Form:	Injection
Strength and Container-Closure:	80 mg prefilled autoinjector (AI) 80 mg prefilled syringe (PFS)
Storage and Handling:	Store refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Do not use TALTZ if it has been frozen. Do not shake

Materials Reviewed:

PFS and AI Container Labels
PFS and AI Carton Labeling



Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

PFS Label

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

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

Autoinjector

(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; *conforms*.
- (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*.
- (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, as the MG statement appears on the 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. *PFS Container Label conforms* (see above).

(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; *conforms.*

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; does not conform.

OBP Request: Revise the statement on the autoinjector label "DO NOT FREEZE" to read "DO NOT FREEZE OR SHAKE".
Applicant revised as requested.

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

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

OBP Requests:

PFS

Add the route of administration statement "For Subcutaneous Use Only" on a single line under the strength statement using bold font. *Applicant revised as requested.*

Add the statement "Single-Dose Only" on a single line under the route of administration statement using bold font. *Applicant revised as requested.*

We concur with DMEPA's recommendation: Relocate the internal code "NL032DAAM02" to appear below the Lilly logo. As currently presented between the Lot and NDC numbers it crowds that area of the label and could be a source of confusion. In addition, the internal code is irrelevant to HCP and patients; therefore, it should not be placed on a prominent position on the label. *Applicant revised as requested.*

Autoinjector

Relocate the route of administration statement "For Subcutaneous Use Only" below the dosage form "injection" and increase its prominence by bolding. *Applicant revised as requested.*

Add the statement "Single-Dose Only" where the route of administration statement is currently presented using bold font. *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; *conforms*.

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

L. 21 CFR 201.100 Prescription drugs for human use. *conforms*.

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*.
- b) The name, addresses, and license number of manufacturer; *conforms*.
- c) The lot number or other lot identification; *conforms*.
- d) The expiration date; *conforms*.
- e) 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*.
- f) The number of containers, if more than one; *conforms*.
- g) 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; *conforms*.
- h) The recommended storage temperature; *conforms*.
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *conforms*.
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.
- m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.
- o) The adjuvant, if present; *not applicable*.
- p) The source of the product when a factor in safe administration; *not applicable*.
- q) 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*.
- r) 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*.
- s) 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)]. *Taltz (ixekizumab) is a monoclonal antibody, therefore is exempt.*

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

D. 21 CFR 610.64 Name and address of distributor; *not applicable*.

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.

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

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

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; *conforms*.

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; *does not conform*.

OBP Requests:

Principal Display Panel (PDP)

Relocate the route of administration statement "For Subcutaneous Use Only" on a single line under the strength statement using bold font. *Applicant revised as requested.*

Add the statement "Single-Dose Only" on a single line under the route of administration statement using bold font. *Applicant revised as requested.*

We concur with DMEPA's request to increase the prominence of the net quantity statement (e.g. ## single-dose prefilled autoinjector and ## single-dose prefilled syringe) by using a larger font and bolding to adequately differentiate between the different package sizes. Consider relocating to a more prominent location on the PDP. *Applicant revised as requested.*

Side panels

Increase prominence of the route of administration statement on the principal display panel (PDP), For Subcutaneous Use Only, by bolding and relocating to appear below the strength, 80 mg/mL. *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; *conforms*.
- 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 of ingredients according to the following:

- Revise "mg/mL" in the list of ingredients to read "mg".
- Revise Sodium Chloride from (b) (4) mg to 11.69 mg to be consistent with PI.
- Delete the trailing zero from "0.30 mg/mL". For example:

Each mL of TALTZ contains 80 mg ixekizumab, Citric Acid Anhydrous, USP (0.51 mg); Polysorbate 80, USP (0.3 mg); Sodium Chloride, USP (11.69 mg); Sodium Citrate Dihydrate, USP (5.11 mg); and Water for Injection, USP.

Applicant revised as requested.

Conclusions:

The container labels and carton labeling for Taltz (ixekizumab) 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 (USP), USP 38/NF 33 [December 1, 2015 to April 30, 2016]. Labeling deficiencies were identified and resolved. The AI container label submitted on December 14, 2015; and the PFS container label and carton labeling (AI and PFS) submitted on February 3, 2016 are acceptable (see below).

Memorandum

To: BLA 125521
Sponsor: Eli Lilly
Trade name: TALTZ
Generic name: ixekizumab
Indication: moderate to severe plaque psoriasis

From: Jill C Merrill, PhD, reviewing toxicologist, DDDP

Through: Barbara Hill, PhD, Pharmacology/Toxicology Supervisor, DDDP

Re: Sponsor's labeling edits

Background: The sponsor of TALTZ submitted a regulatory response to FDA's draft labeling edits (SDN 32; submitted: 12-14-2015) to the above referenced BLA that contains their proposed labeling edits. The portions of the label that contain edits pertaining to nonclinical information are listed below. Sponsor proposed additions are indicated by underlined text and sponsor-proposed deletions by ~~strike through text~~.

8 USE IN SPECIFIC POPULATIONS**8.1 Pregnancy**Risk Summary

There are no available data on TALTZ use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, TALTZ may be transmitted from the mother to the developing fetus. An embryofetal developmental study conducted in pregnant monkeys at doses up to 19 times the maximum recommended human dose (MRHD) revealed no evidence of harm to the fetus

(b) (4)

(b) (4)

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2- to 4% and 15- to 20%, respectively.

DataAnimal Data

An embryo-fetal development study was conducted in cynomolgus monkeys administered ixekizumab. No malformations or embryo-fetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis to near parturition at doses up to

19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD from the beginning of organogenesis to parturition. Neonatal deaths occurred in the (b) (4) offspring of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). These neonatal deaths were attributed to early delivery, trauma, or congenital defect (b) (4); The (b) (4) clinical significance of these findings (b) (4) unknown. No ixekizumab-related effects on (b) (4) functional or immunological development were observed in the infants from birth through six 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of ixekizumab in human milk, the effects on the breastfed infant, or the effects on milk production. Ixekizumab was detected in the milk of lactating cynomolgus monkeys. (b) (4)

(b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TALTZ and any potential adverse effects on the breastfed infant from TALTZ or from the underlying maternal condition.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds with the interleukin 17A (IL-17A) cytokine (b) (4) and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Ixekizumab inhibits the release of proinflammatory cytokines and chemokines.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TALTZ. Some published literature suggests that IL-17A directly promotes cancer cell invasion (b) (4), whereas other reports indicate IL-17A promotes T-cell mediated tumor rejection. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm analysis were observed in sexually mature cynomolgus monkeys that were administered ixekizumab for 13 weeks at a subcutaneous dose of 50 mg/kg/week (19 times the MRHD on a mg/kg basis). The monkeys were not mated to evaluate fertility.

Discussion:

The following discussion of the sponsor's revised label includes recommendations based on Agency discussions for Section 8.1 (Risk Summary, Data) and Section 13.1 (Carcinogenesis).

Section 8.1

Risk Summary

Based on Agency discussions the congenital defect and early deliveries noted in the peri- and post-natal development study are considered drug related and warrant inclusion in the Risk Summary.

Lehla Sahin (DPMH) disagreed with the sponsor's edits to the first paragraph of the Risk Summary, citing the PLLR Guidance.

Data

In the accompanying Regulatory Response Document (Section 4.6) the sponsor provides further details concerning the four neonatal deaths that occurred during the pre- and post-natal development study. One 5 mg/kg female had no milk at the first lactation check and the offspring was euthanized. Another offspring in the 5 mg/kg group had a congenital defect and was euthanized. One offspring in the 50 mg/kg group was delivered early (GD 145) and although the adult female (3502) had milk at the PPD1 lactation check, she was no longer producing milk when examined on PPD5 and the infant was subsequently euthanized (data in study records maintained at the Testing Facility). One 50 mg/kg offspring was found dead on BD1. Although no LY2439821-related changes in infant parameters were observed, external and skeletal examination of the infant revealed traumatic injuries. This information supports the sponsor's addition of the causes of death during this study. (b) (4)

(b) (4). The lack of ixekizumab-related effects has been reduced to functional and immunological development.

Section 8.2

Lehla Sabin (DPMH) commented that transfer of antibodies into breast milk had been discussed at labeling meetings and the Clinical review team considered it

intended to diminish risk. The Clinical review team will determine the acceptability of the sponsor's added text.

Section 12.1

Data from the study report # bTDR131 (In vitro binding kinetics of LY2439821 for human IL-17A/F heterodimer: Surface plasmon resonance analysis) (b) (4)

(b) (4). Although the sponsor's addition is supported by the available nonclinical data, binding affinities are not usually included in labels and may provide an inaccurate marketing advantage if included here. Pharmacology/Toxicology supports deleting it.

Section 13.1

The accompanying Regulatory Response Document (Section 4.9) provided by the sponsor discusses multiple examples of in vivo studies suggesting IL-17 promotes cancer cell invasion and supports deleting (b) (4) from the statement in Section 13.1. However, further Agency discussions determined that the wording in Section 13.1 needs to be modified to convey that the carcinogenic potential of TALTZ exposure has not been evaluated.

The recommended revisions for the nonclinical portions of the TALTZ label are provided below. Proposed additions are indicated by underlined text and proposed deletions by ~~strike through text~~. The recommended revisions are provided based on a clean version of the appropriate sections of the label that have incorporated the sponsor's suggested edits.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TALTZ use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, TALTZ may be transmitted from the mother to the developing fetus. ~~An embryo/fetal developmental study conducted in~~ (b) (4)
(b) (4) pregnant monkeys (b) (4)

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

An embryofetal development study was conducted in cynomolgus monkeys administered ixekizumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis to near parturition at doses up to 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD from the beginning of organogenesis to parturition. Neonatal deaths occurred in the offspring of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). These neonatal deaths were attributed to early delivery, trauma, or congenital defect. (b) (4) The (b) (4) (b) (4) clinical significance of these findings (b) (4) is unknown. No ixekizumab-related effects on (b) (4) functional or immunological development were observed in the infants from birth through 6 months of age.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds with the interleukin 17A (IL-17A) cytokine (b) (4) and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Ixekizumab inhibits the release of proinflammatory cytokines and chemokines.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of TALTZ. Moreover published literature is mixed on potential effects on malignancy risk due to the pharmacologic activity of TALTZ, which is to inhibit activity of IL-17A. Some published literature suggests that IL-17A directly promotes cancer cell invasion, suggesting a potential beneficial effect by TALTZ, whereas other reports indicate IL-17A promotes T-cell mediated tumor rejection, suggesting a potential adverse effect by TALTZ. However, neutralization of IL-17A with TALTZ has not been studied in these models. Depletion of IL-17A with a neutralizing antibody inhibited tumor development in mice, suggesting a potential beneficial effect by TALTZ. The relevance of experimental findings in mouse models for malignancy risk in humans is unknown.

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm analysis were observed in sexually mature cynomolgus monkeys that were administered ixekizumab for 13 weeks at a subcutaneous dose of 50 mg/kg/week (19 times the MRHD on a mg/kg basis). The monkeys were not mated to evaluate fertility.

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/s/

JILL C MERRILL
01/13/2016

BARBARA A HILL
01/13/2016

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum: December 29, 2015
Requesting Office or Division: Division of Dermatology and Dental Products
Application Type and Number: BLA 125521
Product Name and Strength: Taltz (ixekizumab) Injection, 80 mg/mL
Submission Date: December 14, 2015
Applicant/Sponsor Name: Eli Lilly and Company
OSE RCM #: 2015-797-1
DMEPA Primary Reviewer: Carlos M Mena-Grillasca, RPh
DMEPA Team Leader: Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

The Division of Dermatology and Dental Products requested that we review the revised container labels, carton labeling, FPI, and IFUs for Taltz (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

2 CONCLUSION

The revised carton labeling, FPI and IFUs are acceptable; however, the container label for the pre-filled syringe is unacceptable from a medication error perspective. The revised PFS label includes an internal Lilly code “NL032DAAM02” on the top 1/3 of the label, between the lot and NDC numbers. As the internal Lilly code is nonsensical to HCP and patients, its placement next to the lot number and NDC number can be a source of confusion.

¹ Mena-Grillasca C. Human Factors, Label and Labeling Review for Taltz (BLA 125521). 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); 2015 NOV 12. OSE RCM No.: 2015-797, 2015-844.

3 RECOMMENDATIONS FOR LILLY

We recommend the following be implemented prior to approval of this BLA:

- A. Pre-Filled Syringe Container Label
 - a. Relocate the Lilly code "NL032DAAM02" to appear below the Lilly logo. The internal code is currently presented on the top 1/3 of the label, between the lot and NDC numbers. As the internal code is nonsensical to HCP and patients, its placement next to the lot number and NDC number can be a source of confusion.

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

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/s/

CARLOS M MENA-GRILLASCA
12/29/2015

MISHALE P MISTRY
12/29/2015



Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Pregnancy and Lactation Labeling Rule (PLLR) Labeling and Post-Marketing Requirement (PMR) Review

Date: 11-17-2015

From: Leyla Sahin, M.D.
Medical Officer, Maternal Health Team
Division of Pediatric and Maternal Health

Through: Tamara Johnson, M.D., M.S.
Team Leader, Maternal Health Team
Division of Pediatric and Maternal Health

Lynne L. Yao, M.D.
Director,
Division of Pediatric and Maternal Health

To: Division of Dermatology and Dental Products

Drug: Taltz (ixekizumab) onjection; BLA 125521

Proposed Indication: The treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy

Subject: Pregnancy and Lactation Labeling and Post-marketing Requirement

Applicant: Elli Lily

Materials Reviewed:

- Applicant's proposed labeling
- Applicant's proposed post-marketing study
- Literature review

Consult Question: Please assist with Pregnancy and Lactation Labeling and review of proposed post-marketing study

INTRODUCTION

The applicant submitted a biologic license application (BLA) for Taltz (ixekizumab) injection on March 23, 2015. The proposed indication is treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health (DPMH) on April 24, 2015, to assist with reviewing the Pregnancy and Lactation subsections of labeling and the applicant's proposed post-marketing study.

BACKGROUND

Product Background

Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds to the interleukin-17A cytokine and inhibits its interaction with the IL-17 receptor. Ixekizumab inhibits the release of proinflammatory cytokines and chemokines. TALTZ is produced by recombinant DNA technology in a recombinant mammalian cell line.

Disease Background

Psoriasis affects 2% to 3% of the population, men and women equally.¹ Psoriasis commonly starts during a woman's reproductive years. The disease activity during pregnancy is unpredictable and, therefore, it is possible that treatment may be needed.² Based on limited safety data, current clinical guidelines for management of psoriasis during pregnancy and lactation recommend the following:

- First line: moisturizers and topical steroids (preferably low-medium potency)
- Second line: ultraviolet B phototherapy
- Third line: tumor necrosis factor inhibitors (adalimumab, etanercept, infliximab), cyclosporine, and systemic steroids.¹

Pregnancy and Lactation Labeling Rule (PLLR)

On December 4, 2014, the Food and Drug Administration (FDA) published the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR).³ The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule, to include information about the

¹ Bae Y, Van Voorhees A, Hsu S, et al. Review of treatment options for psoriasis in pregnant or lactating women: From the Medical Board of the National Psoriasis Foundation. *J Am Acad Dermatol* vol 67, Number 3:459-477. 2012.

² Bangsgaard N, Rørbye C, Skov L et al. Treating Psoriasis During Pregnancy: Safety and Efficacy of Treatments. *Am J Clin Dermatol*. 2015 Jul 7. [Epub ahead of print]

³ Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

risks and benefits of using these products during pregnancy and lactation. The PLLR took effect on June 30, 2015. The recommendations in this review are consistent with the PLLR format.

DISCUSSION OF LABELING

No publications on the safety of ixekizumab in pregnancy or lactation were found in the literature. In addition, there is no published pregnancy or lactation safety data on secukinumab, an IgG1 IL 17A inhibitor approved in January 2015.

For the Lactation subsection the applicant proposed the inclusion of a statement (b) (4)
(b) (4)
(b) (4) DDDP felt that this statement diminishes
any potential risk due to breastfeeding (b) (4)

(b) (4) Limited published data on infliximab, an IgG1 monoclonal antibody specific for tumor necrosis factor alpha (TNF α) suggest that drug milk levels are very low (undetectable to (b) (4) of the maternal serum concentration).⁴ A recent published review of TNF α inhibitors in pregnancy and lactation states that concentrations of infliximab and adalimumab in breast milk are significantly lower than maternal serum levels, however “a deleterious effect of this exposure on the neonate, although unlikely, cannot be excluded.”⁵ Because there are no available lactation data on ixekizumab, DPMH concurs with DDDP’s preferred approach to state that there are no available data and that the benefits of breastfeeding should be considered with the need for the drug.

CONCLUSION

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR.

DPMH LABELING RECOMMENDATIONS

DPMH participated in a labeling meeting with DDDP on October 16, 2015.

See final labeling for all of the labeling revisions negotiated with the applicant.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no (b) (4) data on ixekizumab use (b) (4) to inform any drug-associated risks. (b) (4) are known to cross the placental barrier; therefore, TALTZ may be transmitted from the mother to the developing fetus. (b) (4)

⁴ LactMed database <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>

⁵ Gisbert JP, Chaparro M. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease. Am J Gastroenterol. 2013;108:1426-38.

The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

An embryofetal development study was conducted in cynomolgus monkeys administered ixekizumab. No malformations or embryofetal toxicity were observed in fetuses from pregnant monkeys administered ixekizumab weekly by subcutaneous injection during organogenesis at doses up to 19 times the MRHD recommended human dose (on a mg/kg basis of 50 mg/kg/week). Ixekizumab crossed the placenta in monkeys.

In a pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of ixekizumab up to 19 times the MRHD from the beginning of organogenesis to parturition. Neonatal deaths occurred in the infants of two monkeys administered ixekizumab at 1.9 times the MRHD (on a mg/kg basis of 5 mg/kg/week) and two monkeys administered ixekizumab at 19 times the MRHD (on a mg/kg basis of 50 mg/kg/week). (b) (4)

(b) (4). No ixekizumab-related effects on (b) (4) functional or immunological development of were observed in the infants from birth through six months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of ixekizumab in human milk, the effects on the breast-fed infant, or the effects on milk production. Ixekizumab was detected in the milk of lactating cynomolgus monkeys. (b) (4) The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TALTZ and any potential adverse effects on the breastfed infant from TALTZ or from the underlying maternal condition.

REVIEW OF PMR

The applicant has proposed a post-approval safety study in pregnant women using electronic medical records. No details are included other than a target start date following enrollment of 1,000 pregnant women exposed to Taltz.

DISCUSSION AND CONCLUSIONS

Intended and unintended exposures during pregnancy will likely occur because plaques psoriasis commonly occurs in females of reproductive potential. In addition, safety data regarding exposure during pregnancy are lacking because pregnant women were excluded during ixekizumab's clinical development program, and very limited outcome data are available on the women who became pregnant in the trials. Therefore, post-approval studies to assess outcomes

following exposure in pregnancy are important to help characterize ixekizumab's safety in pregnancy. A pregnancy exposure registry is the Agency's preferred method for post-marketing data collection in pregnant women due to the prospective method of data collection, which minimizes the biases of retrospective data collection.⁶ In addition, pregnancy registries allow collection of patient level detailed data on potential confounders. However pregnancy registries are limited by their lack of power to assess specific (rare) birth defects and the long duration that may be needed to accumulate data. As discussed by the expert panel at the 2014 FDA public meeting on pregnancy registries and other post-approval safety studies in pregnant women, combining two study methods addresses limitations inherent to each study design.⁷ Combining a pregnancy registry with a complementary study with a different study design that relies on large databases may address the potential low enrollment in a registry. Examples of complementary study designs include a retrospective cohort study using electronic medical record or claims data or a case control study.

Of note, a PMR for a pregnancy registry was issued for Stelara (ixekizumab), an IL 12/23 inhibitor manufactured by a different applicant, at the time of approval in 2009. The pregnancy registry for Stelara is being managed by the Organization of Teratology Information Specialists (OTIS) (now called MothertoBaby) as part of their autoimmune diseases registry.

RECOMMENDATIONS FOR THE APPLICANT

DPMH recommends the following PMR language:

FDA has determined that you are required to conduct the following post-approval safety studies in pregnant women:

“A prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Taltz during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

And

An additional study that uses a different study design (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age in women exposed to Taltz during pregnancy compared to an unexposed control population.

For guidance on how to establish a pregnancy exposure registry, the applicant should review

⁶ FDA Guidance for Industry Establishing Pregnancy Exposure Registries

⁷ FDA webpage Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>

*the Guidance for Industry on Establishing Pregnancy Exposure Registries available at <http://www.fda.gov/cder/guidance/3626fnl.htm>. For information on complementary study methods, the applicant should review the FDA webpage *Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting*; Public Meeting <http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm>.*

Draft study protocols should be submitted three months after product approval.”

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/s/

LEYLA SAHIN
11/17/2015

TAMARA N JOHNSON
11/17/2015

LYNNE P YAO
11/18/2015

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

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

Memorandum

Date: November 13, 2015

To: J. Paul Phillips
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)

CC: Melinda McLawhorn, Pharm.D., BCPS, RAC, Team Leader, OPDP

Subject: **BLA 125521
TALTZ (ixekizumab) injection, for subcutaneous use**

On April 6, 2015, DDDP consulted OPDP to review the draft Package Insert (PI), carton and container labeling, Medication Guide (MG), and Instructions for Use (IFUs) for TALTZ (ixekizumab) injection, for subcutaneous use (Taltz) for the original BLA submission.

OPDP reviewed the proposed substantially complete version of the PI provided by DDDP via e-mail on October 30, 2015. OPDP also reviewed the proposed carton and container labeling submitted to the electronic document room by the sponsor on March 23, 2015. The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the MG and IFUs for Taltz under separate cover. OPDP's comments on the PI and carton and container labeling are provided below.

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
11/13/2015

**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: November 13, 2015

To: Kendal Marcus
Director
Division of Dermatology and Dental Products (DDDP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

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

From: Nathan Caulk, MS, BSN, RN
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 (IFUs)

Drug Name (established name): TALTZ (ixekizumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 125521

Applicant: Eli Lilly and Company

1 INTRODUCTION

On March 23, 2015, Eli Lilly and Company submitted for the Agency's review an original Biologics License Application (BLA) 125521 for TALTZ (ixekizumab) injection. The purpose of this Application is to propose the indication for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy for TALTZ (ixekizumab) injection.

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 April 6, 2015, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for TALTZ (ixekizumab) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs was completed on November 12, 2015.

2 MATERIAL REVIEWED

- Draft TALTZ (ixekizumab) injection MG and IFUs received on March 23, 2015, and received by DMPP and OPDP on April 6, 2015.
- Draft TALTZ (ixekizumab) injection Prescribing Information (PI) received on March 23, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 30, 2015.

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 APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Arial font, size 10.

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)

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 is 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.

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/s/

NATHAN P CAULK
11/13/2015

TARA P TURNER
11/13/2015

BARBARA A FULLER
11/13/2015

LASHAWN M GRIFFITHS
11/13/2015

HUMAN FACTORS, 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:	November 12, 2015
Requesting Office or Division:	Division of Dermatology and Dental Products
Application Type and Number:	BLA 125521
Product Name and Strength:	Taltz (ixekizumab) Injection, 80 mg/mL
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Eli Lilly and Company
Submission Date:	March 23, 2015
OSE RCM #:	2015-797 2015-844
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Kendra Worthy, PharmD
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

This review responds to a request from DDDP to evaluate the results of the Human Factors Study for Taltz (ixekizumab) injection and the container labels and carton labeling for areas of vulnerabilities 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. An FDA Adverse Event Reporting System (FAERS) search was not conducted for this supplement because this is a new drug/device combination product.

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

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant is proposing to market Taltz in a pre-filled syringe (PFS) and an autoinjector (AI). Lilly performed Human Factors studies on the PFS and AI to demonstrate that they could be used safely and effectively by the intended users.

DMEPA had previously reviewed the Human Factors protocols submitted by the Applicant and found the study design acceptable (see Appendix B –Previous DMEPA Reviews).

The applicant was originally pursuing Instructions for Use (IFU) and Quick Reference Guides (QRG) for the Autoinjector; however, due to the high number of failures observed with the use of the QRG, the applicant is no longer pursuing the QRG for the AutoInjector.

There were a total of 9 failures with the AutoInjector as summarized below:

Test Scenario	Failure Mode	No. of Failures	Root Cause
Unassisted Use/ Untrained	Does not remove cap	4 (2 participants x 2 injection attempts)	<p>Participant #1 - Only used the QRG. Confusion during task. His expectation was that the cap would be at the top of the device</p> <p>Participant #2. Used the QRG for the first injection and the IFU for the second injection. English is his second language. The participant's failure to understand the dependent clause "until you are ready to inject" seemed to be the main reason for not uncapping the device. The applicant identified the lack of prominence of the statement "twist off the base cap" as a possible contributing factor.</p> <p><i>DMEPA will recommend that the applicant provide better 'zoomed in' image for step 2a of the IFU.</i></p>
Unassisted Use	Early activation (pushed button before placing the AI on the skin)	2 Participant #1 was untrained Participant #2 was trained	<p>Participant #1 - Did not use either the QRG or the IFU. Inadvertently activated the device. Immediately conveyed understanding of the proper operation. Could not cite any specific deficiency with the device design that resulted in the error.</p> <p>Participant #2 - Did not use either the QRG or the IFU. He didn't think the device was unlocked because his expectation was to hear a click when he turned the lock ring.</p>
Unassisted Use/ Untrained	Early lift off (removed device from injection site before injection was complete)	1	The participant referred to the QRG during the first injection only; did not refer to either the QRG or the IFU during the second injection. The participant misremembered the information from the QRG and a conflicting mental model from previous experiences with other injection devices.
Directed Use/ Untrained	Does not unlock the device	1	<p>The participant referred to the IFU. Participant indicated that she could not determine if the AI was unlocked and thought it was broken.</p> <p><i>DMEPA will recommend that the applicant increase the size of the lock/unlock image on the container label and provide better 'zoomed in' images for steps 2a and 2c of the IFU.</i></p>
Directed Use/ Untrained	Does not fully press the button	1	The participant successfully unlocked the AI but was unable to activate the device. After a few attempts and feeling discomfort in fingers/hand and frustrated she abandoned the task. The participant seemed to know how to use the device and attempted to use it correctly, but thumb fatigue contributed to the task failure.

Failures of not removing the cap, early activation, and early lift off, seen with the AI are no different than failures that are observed with currently marketed AI. In addition, the two instances of early activation occurred during the first injection attempt. During the second injection attempt the participants self-corrected. We note that there was one instance of failure (1 participant) of not unlocking the device or not fully pressing the button that are deemed unique to the proposed AI. We recommend changes to the IFU to improve the prominence of this information (lock/unlock device) to mitigate some of the residual errors observed. Additionally, since the proposed indication is for a chronic disease we expect some of these errors to be self-corrected with subsequent use, as seen in the case of some observed failures where the participants self-corrected in the second attempt.

There were a total of 3 failures with the PFS as described below:

Failure Mode	Number of Failures	Root Cause
Does not remove cap	1	Subject did not refer to the QRG as instructed. Attentional error
Primed device	1	Reliance on transfer from existing mental model (previous experiences with syringes)
Removed, then reinserted the syringe to complete the injection	1	Subject reaction to failure. The participant had inserted the needle, then realized she didn't pinch the skin. Removed the needle from the skin to perform the task correctly.

Failure of not removing the cap does not present unique concerns with the PFS. However, we note that one injection experienced participant primed the PFS on her second injection attempt. The participant indicated that "she had pushed harder than she had intended as a previously trained phlebotomist she was told to prime before any injection". It is unclear why she did not prime the PFS during the first injection attempt. The participant was applying general knowledge for the administration of injectable drugs in vials. The proposed PFS is no different than currently marketed PFS in that it does not require priming. Therefore, this error is due to transfer of existing mental model and cannot be further mitigated. Finally, one participant failed to pinch the skin during the injection. Although she had already inserted the needle when she noticed that she didn't follow the instructions from the IFU correctly, when she tried to self-correct she withdrew the needle resulting in fluid loss. She then proceeded to pinch the skin and re-inject. This error was precipitated by the participants intent on following the IFU and self-correcting even though she had already inserted the needle and was in the process of injecting the fluid. We expect this error to be self-corrected on subsequent use.

Upon review of the container label and carton labeling submitted by the applicant, we noted the following areas for improvement:

- In some places the established name is not commensurate in prominence to the proprietary name as per CFR 201.10(g)(2)
- The net quantity statement on the carton labeling is not prominent and makes it difficult to distinguish between the different package sizes (i.e. 1 vs. 2 vs. 3 PFS and AI).
- The prominence of important information (e.g. For Subcutaneous Use Only, Single-Dose Only) can be improved.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the applicant has demonstrated that Taltz PFS and AutoInjector can be used safely and effectively by the intended users and the residual risks cannot be further mitigated.

We recommend the following be implemented prior to approval of this BLA:

4.1 RECOMMENDATIONS FOR LILLY

- A. General Comments (All Container Label and Carton Labeling)
 - 1. Ensure that the established name is at least ½ the size of the proprietary name and commensurate in prominence to the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). This applies to all packages and all places where the proprietary name, established name, dosage form and strength are presented.
- B. Container Label (Pre-filled Syringe)
 - 1. Add the route of administration statement “For Subcutaneous Use Only” on a single line under the strength statement using bold font.
 - 2. Add the statement “Single-Dose Only” on a single line under the route of administration statement using bold font.
- C. Container Label (Autoinjector)
 - 1. Add the statement “DO NOT SHAKE” following the statement “DO NOT FREEZE”.
 - 2. Relocate the route of administration statement “For Subcutaneous Use Only” below the dosage form and increase its prominence by bolding.
 - 3. Add the statement “Single-Dose Only” where the route of administration statement is currently presented using bold font.
 - 4. Increase the size of the lock/unlock symbols or include the words “lock” and “unlock” next to the symbols. The results of the HF study indicate that these symbols can be overlooked by patients making it difficult for them to assert whether the AutoInjector is in the locked or unlocked position.
- D. Carton Labeling (All Pre-filled Syringe and Autoinjector)
 - 1. Principal Display Panels
 - i. Relocate the route of administration statement “For Subcutaneous Use Only” on a single line under the strength statement using bold font.
 - ii. Add the statement “Single-Dose Only” on a single line under the route of administration statement using bold font.
 - iii. Increase the prominence of the net quantity statement (e.g. ## single-dose prefilled autoinjector and ## single-dose prefilled syringe) by using a larger font and bolding to adequately differentiate between the different package sizes. Consider relocating to a more prominent location on the PDP. As currently presented they are not adequately differentiated.
 - 2. Side panels
 - i. Increase the prominence of the route of administration statement “For Subcutaneous Use Only” by bolding.

E. AutoInjector IFU

1. Step 2a

- i. Revise the image to include a more zoomed-in depiction of the cap removal and of the lock and unlock symbols. The results of the HF study indicate that patients may fail to unlock the device and remove the cap and attempt to perform the injection with the cap on.

2. Steps 2a and 2c

- i. Revise the image to include a better zoomed-in depiction of the lock and unlock symbols. The results of the HF study indicate that patients may fail to unlock the device prior to injection.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Taltz that Lilly submitted on March 23, 2015.

Table 2. Relevant Product Information for Taltz	
Initial Approval Date	n/a
Active Ingredient	Ixekizumab
Indication	Moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	80 mg/mL
Dose and Frequency	160 mg by subcutaneous injection (two 80 mg injections) at week 0, followed by an 80 mg subcutaneous injection at Weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.
How Supplied	80 mg/mL PFS and AutoInjector
Storage	Refrigerated at 2°C to 8°C (36°F to 46°F)
Container Closure	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 1, 2015, we searched the L:drive using the terms Taltz and Ixekizumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified four previous relevant reviews/meeting minutes:

- Type C Guidance Meeting Teleconference¹
- 2013-1751² - Human Factors Protocol Review.
- 2014-568³ - Human Factors Protocol Review.
- 2014-1495⁴ - Human Factors Protocol Review Memo.

The applicant addressed all DMEPA's recommendations for the Human Factors protocols prior to implementation.

¹ Division of Dermatology and Dental Products Type C Meeting Minutes. Silver Spring (MD): FDA, CDER, OND, DDDP (US); 2012 NOV 13.

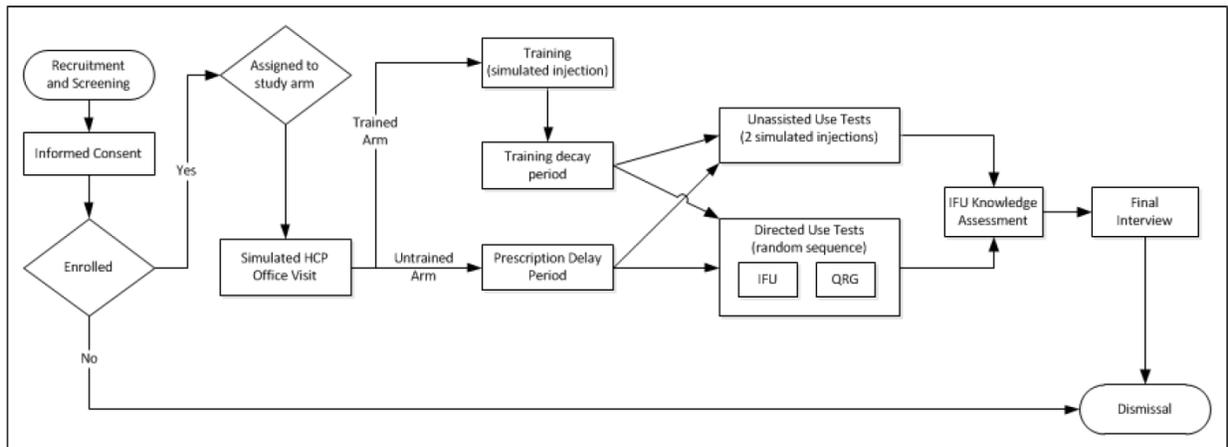
² Mena-Grillasca, C. Human Factors Protocol Review for Tabalumab and Ixekizumab (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 AUG 08. RCM No.: 2013-1751.

³ Mena-Grillasca, C. Human Factors Protocol Review for Ixekizumab and Tabalumab (IND 100834, (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 MAR 31. RCM No.: 2014-568.

⁴ Mena-Grillasca, C. Human Factors Protocol Review Memo for Ixekizumab and Tabalumab (IND 100834, (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 AUG 26. RCM No.: 2014-1495.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Summative Study Design



Pre-Filled Syringe Study Participants:

Group	Stratification	Number Enrolled
Patients (b) (4)		(b) (4)
	Psoriasis (Ps)	21*
Caregivers		23
HCPs		16

*19 of these patients suffered from 2 or 3 of these conditions

AutoInjector Study Participants:

The study population included 119 participants who were representative of the intended user population, and included:

[n=84] Patients (≥18 years old) who report they have been diagnosed by an HCP with:

- (b) (4)
- [n=15] Psoriasis (PS) and self-report that they have a minimum affected body surface area greater than approximately 10%,

(b) (4)

[n=17] Caregivers (≥18 years old) with no professional healthcare-related training who are currently responsible for the care of either other adults or juveniles. Caregivers may include relatives (e.g., parents, spouses, or children), friends, or neighbors of Patients.

[n=18] HCPs (≥18 years old) who diagnose, treat, administer injections, or provide training to individuals with (b) (4) PS, (b) (4)

AutoInjector Patient and Caregiver Demographics

Table 9: Validation Study – Patient and Caregiver Demographic Summary

Characteristic	Stratification	n
Age	18-40 years	16
	41-60 years	57
	≥61 years	28
Gender	Male	32
	Female	69
Injection Experience	Naïve	33
	Experienced	68
Functional Impairments*	Hand (M-SACRAH >20)	46
	Vision (VF-14 ≤75)	5
	Colorblind	2
	None	52

*Note: Includes 4 participants who had 2 impairments each (3 participants with hand and vision impairments, 1 participant with hand impairment and colorblindness)

C.2 Results

Pre-Filled Syringe

Pre-Filled Syringe – Summary of Task Success

Subjects	n	Injection Attempts	Task Successes	Task Failures	% Success	% Failure
Patients	79	158	155	3	98%	2%
Caregivers	23	46	46	0	100%	0%
HCPs	16	32	32	0	100%	0%
Totals	118	236	233	3	99%	1%

Pre-Filled Syringe – Observed Use Problems

Priority Use Step	Use Problem	Observation	Instances
Remove Needle Cap	Use Error	Did not remove needle cap	1
	Difficulty	Did not initially remove needle cap	2
Insert the needle into the injection site	N/A	N/A	0
Depress Plunger	Use Error	Primed device	1
	Use Error	Removed, then reinserted syringe to complete injection	1
Remove the needle from the injection site	N/A	N/A	0
Total			5

Pre-Filled Syringe – Root Cause Investigation

Priority Use Step	Use Problem	Observation	Root Cause Determination	Subject
Remove Needle Cap	Use Error	Did not remove needle cap	Attentional Error	S-234
	Difficulty	Did not initially remove needle cap	Negative Transfer from existing Mental Model	S-213
			Device Design	S-222
Insert the needle into the injection site	N/A	N/A	N/A	N/A
Depress Plunger	Use Error	Removed syringe during injection while expelling fluid	Subject Reaction to Error	S-121
	Use Error	Primed device	Reliance on/Negative Transfer from existing Mental Model	S-214
Remove the needle from the injection site	N/A	N/A	N/A	N/A

Pre-Filled Syringe – IFU Knowledge Assessment Results

#	Question	Correct Answers	Incorrect Answers
1	“Before you administer the injection, what supplies do you need to get?” <i>(Required answer: Section 1B, “Sharps Container”)</i>	114	4
2	“After you take the device out of the refrigerator, how long do you have to wait before using the product?” <i>(Required answer: Section 1A, “30 minutes”)</i>	118	0
3	“If you wanted to warm the medicine before injecting, is it ok to use hot water?” <i>(Required answer: Section 1A, “No”)</i>	113	5
4	“Once you’ve gathered your supplies, what do the instructions tell you about inspecting the device before use?” <i>(Required answer: Section 1C “Check expiration date, check for damage, check medicine.”)</i>	115	3
5	“What was the lot number and expiration date (on the device)?” <i>(Required answer: “01 Feb 2016”)</i>	112	6
6	“Where can you inject?” <i>(Required answer: Section 1E “Abdomen, thigh, or back of arm.”)</i>	115	3
7	“What do you do with the cap after you pull it off the device?” <i>(Required answer: Section 2A “Discard needle cap.”)</i>	114	4
8	“What do the instructions tell you about disposing the syringe?” <i>(Required answer: Section 3A “Dispose in Sharps Container.”)</i>	116	2
Totals:		917	27
Overall:		n=118	3% error

Autolinjector

Use-Errors Unassisted-Use Scenario

Use Error	Instances
Does not remove cap (attempts injection with cap on)	4*
Pushes injection button before placing on skin (early activation)	2
Removes device from injection site before injection complete (early liftoff)	1
Total	7

*Note: These 4 instances were by 2 participants (each participant experienced the same error on both tasks)

Training Arm	User Group	n	Task Failures				Failure Rate by Training
			1 st Injection		2 nd Injection		
			Instances	Rate	Instances	Rate	
Trained (n=31)	Patients	21	1	5%	0	0%	1/62 (2%)
	Caregivers	8	0	0%	0	0%	
	HCPs	2	0	0%	0	0%	
Untrained (n=32)	Patients	20	3	15%	3	15%	6/64 (9%)
	Caregivers	3	0	0%	0	0%	
	HCPs	9	0	0%	0	0%	
Subtotal		63	4	6%	3	5%	
Total		126	7 (6%)				

Use-Errors Directed-Use Scenarios

Use Error	IFU	QRG
Removes device from injection site before injection complete (early liftoff)	0	3
Does not unlock (no activation)	1	1
Does not remove cap (attempts injection with cap on)	0	2
Pushes injection button before placing on skin (early activation)	0	2
Places auto-injector upside down/ potential inverted injection	0	1
Does not fully press button (no dose delivered)	1	0
Subtotal	2	9
Total	11	

Training Arm	User Group	n	Task Failures				Failure rate by Training
			IFU		QRG		
			Instances	Rate	Instances	Rate	
Trained (n=21)	Patients	14	2	14%	1	7%	3/42 (7%)
	Caregivers	3	0	0%	0	0%	
	HCPs	4	0	0%	0	0%	
Untrained (n=35)	Patients	29	0	0%	7	24%	8/70 (11%)
	Caregivers	3	0	0%	0	0%	
	HCPs	3	0	0%	1	33%	
Subtotal		56	2	4%	9	16%	
Total		112	11 (10%)				

IFU Knowledge Assessment – Summary of Incorrect Responses

IFU Question	Incorrect Answers		
	Patients (n=84)	Caregivers (n=17)	HCPs (n=18)
[1] According to these instructions, how long should you wait after you get your device from the refrigerator before you use it?	0	0	0
[2] What do these instructions tell you about the supplies you'll need for your injection?	1	0	0
[3] What do these instructions tell you about checking the expiration date?	1	0	0
[4] What do these instructions tell you about inspecting for damage?	1	0	0
[5] What do these instructions tell you about the injection sites you should use?	0	0	0
[6] According to these instructions, how should you dispose of a used device?	0	0	0

Summary of Potential Design-Related Root Causes

Root Cause Type	Use Problem	Task	Root Cause
Potential device-related (n=11)	(0) use errors (9) difficulties*	(9) unassisted use test (0) directed use test	(3) Difficulty waiting for injection (impatience) (2) Difficulty hearing clicks (1) Difficulty knowing how firmly to hold in place (1) Difficulty pushing injection button (1) Difficulty reading expiration date (1) Difficulty inspecting medicine through window (1) Difficulty unlocking auto-injector (1) Difficulty viewing device lock/unlock icons
Potential IFU-related (n=1)	(1) use error (0) difficulties	(1) unassisted use test (0) directed use test	(1) IFU Step 2a: direction to remove base cap not sufficiently prominent
Potential QRG-related (n=13)	(10) use errors (2) difficulties**	(2) unassisted use test (10) directed use test	(5) QRG Step 1: Direction to remove base cap not sufficiently prominent (3) QRG Step 2: Lock/unlock symbols in graphic too small (2) QRG Step 2: Direction to hold the device for 2 clicks not sufficiently prominent (2) QRG Step 2: Does not indicate the importance of holding the device in place (1) QRG Step 1: Inspection step not sufficiently prominent.
Total: 25 root causes (11 device, 1 IFU, 13 QRG)	Total: 22 use problems (11 use errors, 11 difficulties)		

*Note: 2 reported difficulties each involved 2 root causes. Refer to participants #01008 and #02002 in Table 17.

**Note: 1 reported difficulty involved 2 root causes. Refer to participant #02035 in Table 17.

Validation Study – Key Findings and Outcomes

Key Findings	Conclusions
<p>[1] Device: There were no (0) observed use errors and nine (9) reported difficulties attributable to the auto-injector design, which were random in nature (i.e., do not establish a pattern), and do not indicate additional modifications of the auto-injector interface which would be likely to further reduce risks.</p> <p>[2] Carton: There were no (0) observed use problems attributable to the carton design.</p> <p>[3] IFU: There was one (1) random use error attributable to the IFU design, that does not establish a pattern, and does not indicate additional modifications of the IFU which would be likely to further reduce risks.</p> <p>[4] QRG: There were ten (10) observed use errors and two (2) reported difficulties attributable to the QRG design, including five (5) instances in which the QRG direction to remove the base cap (Step 1) was not sufficiently prominent, and three (3) instances in which the lock/unlock symbols in the QRG Step 2 graphic were too small. The results suggest a pattern of preventable failures or difficulties which could be further reduced or eliminated through additional modifications of the QRG.</p>	<p>With respect to use safety:</p> <p>[1] The (b)(4) Auto-injector device, carton, and IFU meet acceptance criteria and therefore are considered validated.</p> <p>[2] The (b)(4) Auto-injector QRG does NOT meet acceptance criteria and therefore is NOT considered validated.</p>

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F.

N/A

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

/s/

CARLOS M MENA-GRILLASCA
11/12/2015

LUBNA A MERCHANT on behalf of KENDRA C WORTHY
11/12/2015

LUBNA A MERCHANT
11/12/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: November 2, 2015

TO: J. Paul Phillips, Regulatory Project Manager
Jane Liedtka M.D., Medical Officer
Jill Lindstrom, M.D., Medical Team Leader
Division of Dermatologic and Dental Products

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

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

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125521

APPLICANT: Eli Lilly and Co.

DRUG: Taltz [ixekizumab (solution for injection)]

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of plaque psoriasis

CONSULTATION REQUEST DATE:	April 29, 2015
CLINICAL INSPECTION SUMMARY DATE:	October 16, 2015
DIVISION ACTION GOAL DATE:	March 8, 2016
PDUFA DATE:	March 23, 2016

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Taltz for the treatment of plaque psoriasis.

The pivotal studies I1F-MC-RHBC entitled, “A 12-Week Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of LY2439821 to Etanercept and Placebo in Patients with Moderate to Severe Plaque Psoriasis with a Long-Term Extension Period”, and I1F-MC-RHAZ entitled, “A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Induction Dosing Period Followed by a Randomized Maintenance Dosing Period and a Long-Term Extension Period to Evaluate the Efficacy and Safety of LY2439821 in Patients with Moderate-to-Severe Plaque Psoriasis”, and I1F-MC-RHBA entitled, “A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Comparing the Efficacy and Safety of LY2439821 to Etanercept and Placebo in Patients with Moderate-to-Severe Plaque Psoriasis” were inspected in support of this application.

Dr. Blauvelt’s site was selected for inspection because of its participation in two trials (RHAZ and RHBC) and because the results were not consistent across trials (TALTZ 80 mg Q2W: 93% vs 79% / TALTZ 80 mg Q4W: 86% vs. 56%).

Dr. Bukhalo’s site was selected for inspection because of its participation in two trials (RHAZ and RHBC) and because the results for etanercept (an approved product for this indication) were very low (i.e., 8% for success on sPGA). In addition, the results for the TALTZ treatment arms were also much lower than the overall average.

Dr. Birbara’s site was selected for inspection for Trial RHBA because the results for all three active treatment arms were very low, especially for etanercept (i.e., 9% for success on sPGA).

II. RESULTS (by Site):

Name of CI/ Address/ Contact Information	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Blauvelt, Andrew 9495 SW Locust St, Suite G Portland, OR 97223 Phone: 503-245-1525 Fax: 503-245-0315 email: blauvelt.omrc@comcast.net	I1F-MC-RHBC/ 102/ 52 and I1F-MC-RHAZ/ 102/ 40	14 Jul-10 Aug 2015	VAI
Bukhalo, Michael Altman Dermatology 1100 W. Central Road, Suite 200 Arlington Heights, IL 60005 Phone: 847-392-5440 Fax: 847-385-0294 email: bukhalom@hotmail.com	I1F-MC-RHBC/ 103/ 44 and I1F-MC-RHAZ/ 103/ 36	26 Jun-21 Jul 2015	NAI
Birbara, Charles Clinical Pharmacology Study Group 25 Oak Ave, Suite 246 Worcester, MA 01605 Phone:508-755-0201 Fax:508-755-8909 email:cabirbara@aol.com	I1F-MC-RHBA/ 102/ 38	8-15 Jun 2015	VAI

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.

1. Blauvelt, Andrew9495 SW Locust St, Suite G
Portland, OR 97223

- a. What was inspected:** At this site for Protocol I1F-MC-RHAZ, 42 subjects were screened, 40 subjects were enrolled, two subjects failed screening, and ten subjects discontinued prematurely. For Protocol I1F-MC-RHBC, 59 subjects were screened, 52 subjects were enrolled, seven subjects failed screening, and 16 subjects were discontinued early. Both studies were ongoing at the conclusion of this inspection.

For Protocol IIF-MC-RHAZ, the study records of 12 subjects were reviewed and the informed consent documents of 14 subjects were reviewed. For Protocol IIF-MC-RHBC, the study records of 16 subjects were reviewed and the informed consent documents of 14 subjects were reviewed.

Records reviewed for both studies included, but were not limited to, inclusion/exclusion criteria, primary and secondary efficacy endpoint data, case report forms (CRFs), medical records, laboratory reports, concomitant medications, drug accountability and storage records, financial disclosure forms, and sponsor, monitor, and IRB correspondence.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection with observations noting that the investigation was not conducted in accordance with the investigational plan, that unused supplies of investigational drug were not disposed of in accordance with sponsor instructions, and that case histories were not prepared or maintained accurately. Specific observations include but are not limited to the following:

- Subject 1627 was enrolled in Study RHBC despite prior use of etanercept which is an exclusion criterion.
- Subject 1648 was enrolled in Study RHBC despite evidence or suspicion of active or latent TB; i.e., a positive Quantiferon Gold test.
- Subject 1084 in Study RHAZ was hospitalized for a total hip arthroplasty. This hospitalization was not promptly reported as a severe adverse event (SAE).
- The site used a [REDACTED] (b) (4) [REDACTED] for Study RHAZ that was not approved by the sponsor. The site-specific sPGA form differed from the sponsor-approved sPGA form in that the former rated thickness, erythema, and scaling separately while the latter assigned one overall rating to these three rating elements.

The issue regarding the use of different sPGA forms has been discussed with the reviewing medical officer, the team leader, and with the statisticians. Subsequent statistical analysis demonstrated that exclusion of the data from Dr. Blauvelt's site did not change overall findings (actual results remained the same when rounded to the nearest whole number).

Dr. Blauvelt in his August 27, 2015, written response to the inspection findings, acknowledged his responsibilities to comply with applicable regulations, and responded satisfactorily to the observations on the Form FDA 483. He noted that corrective actions have been put in place to prevent the reoccurrence of the deficiencies noted during this inspection.

c. Assessment of data integrity: Other than the discrepancies noted above, the studies appear to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Bukhalo, Michael
Altman Dermatology
1100 W. Central Road, Suite 200
Arlington Heights, IL 60005

- a. **What was inspected:** At this site for Protocol I1F-MC-RHAZ, 43 subjects were screened, 36 subjects were randomized, and 31 subjects completed the study through Week 60. For Protocol I1F-MC-RHBC, 53 subjects were screened, 46 subjects were randomized, and 39 subjects completed the study through Week 60.

For Protocol I1F-MC-RHAZ, the study records for all 36 randomized subjects were reviewed. Signed informed consent was obtained from all randomized subjects prior to study entry. Source records were compared with data listings. No discrepancies were noted between source documents and line listings with respect to all primary and select secondary efficacy endpoints. Records reviewed included, but were not limited to, regulatory files, financial disclosures, investigational products, sponsor, CRO, and IRB communications, subject eligibility, protocol adherence and deviations, adverse events, concomitant therapies, and test article accountability and storage.

For Protocol I1F-MC-RHBC, the study records for all 46 randomized subjects were reviewed. Signed informed consent was obtained from all randomized subjects prior to study entry. Source records were compared with data listings. No significant discrepancies were noted between source documents and line listings with respect to all primary and select secondary efficacy endpoints. Records reviewed included, but were not limited to, inclusion/exclusion criteria, financial disclosure, sponsor, CRO, and IRB communications, randomization, dosing schedules, adverse events, protocol deviations, and test article accountability and storage.

- 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. Birbara, Charles
Clinical Pharmacology Study Group
25 Oak Ave, Suite 246
Worcester, MA 01605

- a. **What was inspected:** At this site for Protocol IIF-MC-RHBA, 48 subjects were screened, 38 subjects were enrolled, and 12 subjects dropped out of the study. Study source documents were compared with data line listings for verification. The records of 12 subjects were reviewed in depth. All 12 subjects signed informed consent forms prior to screening procedures. Records reviewed included, but were not limited to, financial disclosures, delegation of responsibility, training logs, monitoring logs and reports, subject randomization, primary and secondary efficacy endpoints, adverse events, protocol deviations, and drug accountability.
- b. **General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection noting that the investigation was not conducted in accordance with the investigational plan because Subject 1052 was treated with methotrexate, a protocol-excluded concomitant medication, on a regular basis throughout the study period.

Dr. Birbara in his June 24, 2015, written response to the inspection findings, acknowledged that Subject 1052 was erroneously administered methotrexate on a regular basis in violation of the protocol. Dr. Birbara initiated a review of all subject charts to ensure that all other subjects were not inappropriately administered methotrexate either during the designated washout period or the study.

- c. **Assessment of data integrity:** Other than the deviation noted above, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Blauvelt, Bukhalo, and Birbara were inspected in support of this NDA. Dr. Blauvelt was issued a Form FDA 483 for a number of protocol deficiencies; however, Dr. Blauvelt's written response appeared adequate. In addition, a statistical re-evaluation of the data resulting from the site's use of a different sPGA form demonstrated that there was no significant change to overall findings. The final classification of this inspection was Voluntary Action Indicated (VAI).

Dr. Bukhalo was not issued a Form FDA 483, and the final classification of the inspection was No Action Indicated (NAI).

Dr. Birbara was issued a Form FDA 483 for a protocol deviation involving treatment of a subject with a protocol-excluded medication. Other than this discrepancy, the study appears to have been conducted adequately and the final classification of the inspection was Voluntary Action Indicated (VAI).

In summary, the clinical sites of Drs. Blauvelt, Bukhalo, and Birbara appear to have conducted the studies adequately, and the data generated by these sites appear acceptable in support of the respective indication.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Susan D. Thompson, M.D., for
Janice Pohlman, M.D., M.P.H.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROY A BLAY
11/03/2015

SUSAN D THOMPSON
11/03/2015

KASSA AYALEW
11/03/2015



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: October 24, 2015

From: Lana Shiu, M.D.
General Hospital Devices Branch, DAGRID, ODE, CDRH

To: J. Paul Philips
Division of Dermatology and Dental Products, Office of New Drugs, CDER

Via: Keith Marin and Ryan McGowan
Combination Products Team Leaders, GHDB, DAGRID, CDRH
Rick Chapman
Branch Chief, General Hospital Devices Branch, DAGRID, ODE, CDRH

Subject: BLA 125521 ixekizumab /Applicant: Eli Lilly
EDR: \\CDSESUB1\EVSPROD\BLA125521\125521.enx (SDN-1; eCTD 0000)
CDRH Tracking: ICC1500161

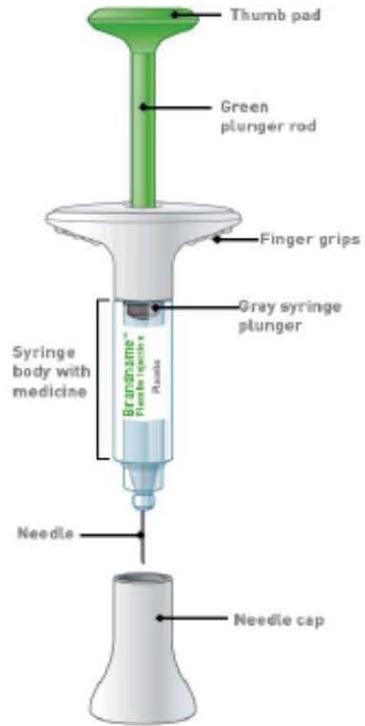
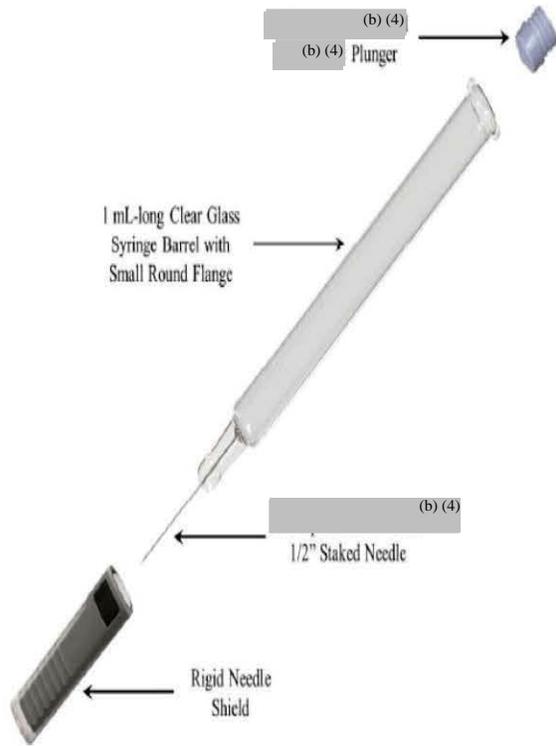
Background: The applicant has now submitted the marketing application (BLA 125521) for ixekizumab 80 mg/mL with two delivery systems: prefilled syringe (PFS) and autoinjector (AI).

Indication for Use: The product is intended to treat adult patients with psoriasis.

PFS Device Description-

The primary container closure system for ixekizumab injection is a 1 mL-long clear glass syringe barrel with (b) (4) staked needle, and closed with a (b) (4) plunger and rigid needle shield.

Table with 2 columns: Component, Description. Rows include Syringe Barrel and Plunger with redacted descriptions.



Ixekizumab Prefilled Syringe

Component/Process	Supplier	Drug / Device Master File Number
Syringe Barrel		(b) (4)
Needle Shield (b) (4)		
Plunger		
		(b) (4)

	Component	Material
Patient Contact Components	Plunger Rod	
	Finger Grips	
	Syringe Body (b) (4)	
	(b) (4)	
	Needle Cap (b) (4)	
Internal Component	Flange Cap	

Ixekizumab Injection Container Closure System Components

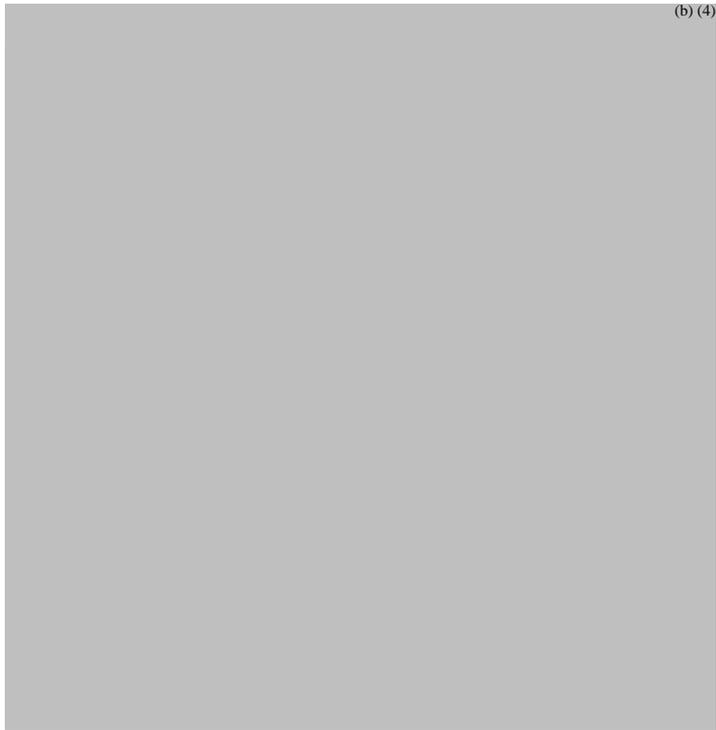
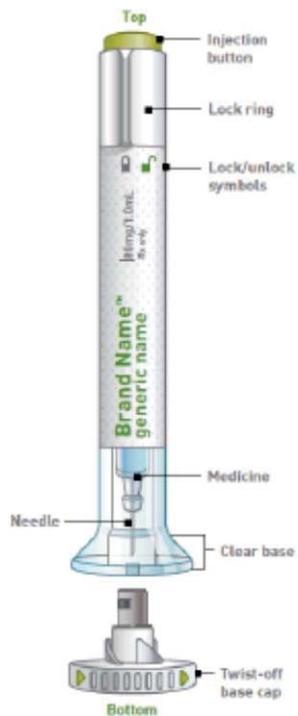
Closure Description	Component	Materials of Construction	Function
(b) (4) clear glass 1 mL-long syringe barrel with small round flange, (b) (4) 1/2" staked needle, and (b) (4) rigid needle shield	(b) (4)	(b) (4)	(b) (4)
(b) (4) (b) (4) plunger			

¹ These two components come together to form the Rigid Needle Shield (RNS)

Barrel Dimensions:

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Autoinjector Device Description



The auto-injector is a prefilled, single-use, injection device that delivers drug product subcutaneously in a fixed-dose format. The auto-injector is intended for use with Lilly parenteral drug products that are filled in a 1-mL glass syringe with a staked needle.

It was developed to enable patients, caregivers or Health Care Professionals (HCP) to administer a subcutaneous injection. The auto-injector Label provides drug product and dosage form information. The activation end incorporates a lock feature to prevent unintentional activation and an Injection Button to start the injection sequence. The injection end of the auto-injector incorporates a Base Cap for needle shield removal and Clear Base for stable positioning at the injection site with 360 degree viewing of the drug product.

The combined semi-finished syringe and auto-injector form a prefilled, single-use injection device that delivers the fixed dose of drug product to the subcutaneous tissue (b) (4). The needle is inserted perpendicular to the skin without the need to raise a skinfold.

The ixekizumab auto-injector is stored in refrigerated conditions and allowed to come to room temperature prior to use.

The injection is user-initiated; however, the auto-injector uses a spring driven mechanism to automate insertion of the needle, deliver the single dose of ixekizumab (b) (4). The autoinjector is properly disposed of after use.

Testing-Biocompatibility—Deficiency Questions generated 9/24/2015

The external auto-injector components, Injection Button, Lock Ring, Device Body / Clear Base, and Base Cap (b) (4) are touched by the user as they operate the device to administer an injection. The Rigid Needle Shield Puller may be touched by the user when the Base Cap is removed. It may take the user up to one minute to perform an injection. The patient may be dosed as frequently as once every two weeks. The delivery device is kept at 2-8°C until it is put in use.

According to the definitions in the ISO standard, the device component of the combination product is classified as a *surface-contacting device in contact with intact skin* where cytotoxicity, irritation and sensitization are indicated.

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Biocompatibility Consult Review for the Prefilled Syringe (PFS) and the Auto-injector Proposed in BLA125521—9/24/2015

The prefilled syringe (PFS):

- The sterilized syringe system, a 1-mL, long glass syringe with a staked needle, is the primary container closure system for ixekizumab. Drug-device contact review of the primary container closure system will be reviewed by the CDER review team and device-patient contact biocompatibility is reviewed here by CDRH.
- The external components of the PFS consist of the plunger rod, finger grips, flange cap, syringe body (casing around the syringe barrel), needle cap, and cap insert components. The external components do not contact the drug product.

- The external components are touched by the user as they administer an injection. It may take the user up to one minute to perform an injection. The patient may be dosed as frequently as once every two weeks. The sponsor indicates that the external components are classified as surface-contacting devices in contact with intact skin.
- The materials used in the PFS exterior components are identified. The sponsor states that the materials selected are commonly used in consumer healthcare products.
- The final (b) (4) external components of the PFS were tested for *in vitro* cytotoxicity, irritation, and sensitization, based on applicable ISO 10993 test standards. Biocompatibility test reports are provided for review.

Reviewer Comments:

- The biocompatibility test reports have been reviewed. All testing is deemed acceptable. I have no question regarding the biocompatibility of the external components of the PFS.

The Auto-injector:

- The sponsor states that the auto-injector does not contact the drug product. The drug remains in the primary container closure ((b) (4) syringe) until the drug is injected. The pre-filled glass syringe with a staked needle is the primary container closure system for ixekizumab. Drug-device contact of the primary container closure system will be reviewed by the CDER review team and autoinjector patient contact is reviewed here by CDRH.
- The external auto-injector components include the Injection Button, Lock Ring, Device Body / Clear Base, and Base Cap (b) (4).
- The external auto-injector components are touched by the user as they operate the device to administer an injection. The Rigid Needle Shield Puller (RNS Puller) may be touched by the user when the Base Cap is removed. It may take the user up to one minute to perform an injection. The patient may be dosed as frequently as once every two weeks.
- The auto-injector is classified as a surface-contacting device in contact with intact skin.

- The materials used in the auto-injector are identified. The sponsor states that the materials selected are commonly used in consumer healthcare products.
- The materials that make up the portions of the delivery device that come into contact with patient were tested for *in vitro* cytotoxicity, irritation, and sensitization, based on applicable ISO 10993 test standards. Biocompatibility test reports are provided for review.

Reviewer Comments:

- The biocompatibility test reports have been reviewed. Please see the recommended deficiencies below.

Recommended ICC1500161 (BLA 125521) Biocompatibility Deficiencies

1. To demonstrate biocompatibility of the auto-injector, you have provided testing of *in vitro* cytotoxicity, irritation, and sensitization using a test device (b) (4). (b) (4) However, you do not provide a clear and detailed description for the (b) (4) and do not justify how the test device represented the final finished subject auto-injector. To determine if the testing provided is appropriate and adequate to support the biocompatibility of the subject device, please provide a valid justification for the test device. Alternatively, please provide revised test reports for each of the biocompatibility testing based on the final finished subject device. Please ensure that all patient contacting device components contained in the subject auto-injector were evaluated for biocompatibility.
2. The test extracts used in the *in vitro* cytotoxicity testing (b) (4) (b) (4) (b) (4) prior to the cytotoxicity testing may invalidate the test results. Without an appropriate justification, it is not acceptable by the FDA. To demonstrate that the cytotoxicity test results are valid, please provide chemical analytical testing data to support (b) (4) (b) (4). Alternatively please provide the cytotoxicity testing (b) (4) (b) (4) .

Eli Lilly provided response on 10/16/2015 via a 22page PDF document:

Lilly Response to Question 1

The ixekizumab auto-injector design was called (b) (4) during development and this name is used in the design history documents. The external components (i.e. patient contacting components) of green button and base cap arrows (b) (4) that

were used in the biocompatibility testing are the same components to be used for the ixekizumab commercial auto-injector. Since contact components of the tested device are the same as the commercial device, the testing provided is appropriate and adequate to support the biocompatibility of the commercial device. No other chemicals are used in the manufacture of the device (e.g. plasticizers, fillers, color additives, cleaning agents, or mold release agents). The test device consisted of the external components of the ixekizumab auto-injector shown in [Figure Q1-1](#) and included the Injection Button, Lock Ring, Device Body / Clear Base, and Base Cap (b) (4)

(b) (4) The Rigid Needle Shield Puller (RNS Puller in [Figure Q1-1](#)) may be touched by the user when the Base Cap is removed.

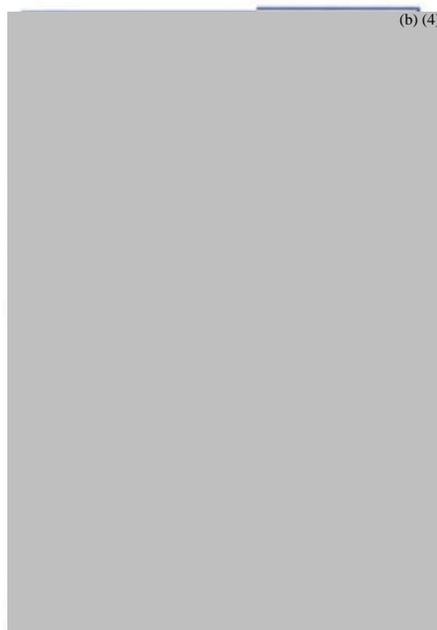


Figure Q1-1 **Ixekizumab auto-injector contact parts**

Lilly Response to Question 2

Lilly repeated the cytotoxicity testing after receiving similar FDA comments on another Lilly product. The Toxikon cytotoxicity test report, 15-00847-G1, (b) (4) is attached. This testing confirmed the test article meets the requirements and is not considered to have a cytotoxic effect.

Final Biocompatibility Recommendation (BLA 125521) -10/23/2015- per Dr. Bifeng Qian

The information provided in the BLA122521-ICC1500161-S002 response is deemed adequate to address the biocompatibility concerns raised in my email dated 9/23/2015. There are no pending biocompatibility deficiencies for the Prefilled Syringe (PFS) and the Auto-injector proposed in [ICC1500161](#) (BLA 125521).

Testing-Clinical Trial (Tracking and Analysis of device malfunctions/breakage, medication errors related to device use or serious adverse events related to the device)

Sponsor reported no SAE (serious adverse events occurred during Study IQBC. The most frequently reported AE deemed device-related by the investigator was injection-site edema and was reported by 2 subjects (3%) in Part A and 1 subject in Part C (7%). These AEs were reported following injections with the auto-injector given by staff members. There were no device-related AEs reported in Part B. There were no AEs following self-administration with the auto-injector, and there was minimal non-injection pain for subjects using the auto-injector.

Overall, there were no clinically significant differences in bruising, bleeding, and the amount of leakage, tenderness, swelling, and erythema with injection into the abdomen, thigh, or upper arm with the auto-injector versus manual injections.

There were no statistically significant or clinically meaningful differences in pain intensity scores between auto-injector and manual injections, and no significant difference in pain scores at any of the injection site locations.

Design Input/Requirement Per ISO 11608:

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Dose Accuracy Testing Results

The auto-injector has been shown to meet the visual, functional and dose accuracy requirements of ISO 11608-1:2012.

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Questions to the sponsor:

- You reported no serious adverse events occurring during your clinical trials. However, did you track/trend/analyze any of the device malfunctions/failures/or medication errors related to the device use? If yes, what were the results and where are they located in the submission?
- There should be a spring component inside the autoinjector assembly. What is the plunger spring force at ambient conditions? Please provide the test protocol, sample size and results.
- In section 3.2.P.8.3 you have provided a 73 page PDF document, we are interested in the autoinjector combination product's device functionality tests under various temperature storage conditions. We have noted that you reported the Injection Time with a acceptance criteria of "pass" and your test results are also reported as "pass" without numerical representation. Please revise your report and specify your injection time acceptance criteria in terms of seconds and express your actual test results also in seconds.
- In section 3.2.P.7 you have provided a 874 page document, where under Engineering Specifications, (b) (4)



(b) (4) We believe that you need to scrutinize the engineering specifications provided in this submission and provide the Agency with the accurate/correct device information.

Response provided by Eli Lilly in May of 2015 to the above questions:

Q1: You reported no serious adverse events occurring during your clinical trials. However, did you track/trend/analyze any of the device malfunctions/failures/or medication errors related to the device use? If yes, provide the results or identify their location in the submission.

Lilly Response to Question 1

The malfunctions, failures and medication errors for the autoinjector were tracked/trended/analyzed in the Clinical Trials and Human Factors studies. The autoinjector was evaluated in Study RHBL and this summary is located in Module 5.3.3.4.

In this study, there was one use issue of reported injection site leakage. The device was investigated and no manufacturing defects or damage was present. This issue is associated with one of two use errors; either removing the device before the injection is complete or a shallow injection caused by not pressing the device firmly against the skin.

Three additional autoinjector complaints were reported that resulted from different isolated assembly errors. One device had a missing Rigid Needle Shield (RNS) puller resulting in failure to remove the RNS prior to device activation. One device had the syringe clip installed over the RNS resulting in failure to remove the RNS. One device had a misalignment of the injection button resulting in difficulty pushing the injection button and activating the device. These assembly errors were addressed through assembly fixture modification and operator retraining prior to device assembly Process Validation.

Q2: There should be a spring component inside the autoinjector assembly. What is the plunger spring force at ambient conditions? Provide the test protocol, sample size and results.

Lilly Response to Question 2

The requirement per the spring drawing/specification is provided

(b) (4)

(b) (4)

Q3: In Section 3.2.P.8.3 you have provided a 73 page document, we are interested in the autoinjector combination product's device functionality tests under various temperature storage conditions. We note that you reported the Injection Time with an acceptance criteria of "pass" and your test results are also reported as "pass" without numerical representation. Revise your report and specify your injection time acceptance criteria in terms of seconds and express your actual test results also in seconds.

Lilly Response to Question 3

In lieu of revising the entire report, the requested numerical data is provided in the following three tables. The data collection system for the injection time test reports a pass/fail result based

upon a statistical analysis of the data. The injection time result at each Time Point is the mean of the injection times for a representative sample from each of assembled autoinjector stability lots.

Batch C274682C

Analytical Property	Unit	Acceptance Criteria	Storage Condition	Time Point (Month)		
				0	1	3
Process Injection Time	Seconds	USL: 10 seconds (A 95% confidence/95% probability content upper tolerance limit is (b) (4))				(b) (4)

Batch C274682D

Analytical Property	Unit	Acceptance Criteria	Storage Condition	Time Point (Month)		
				0	1	3
Process Injection Time	Seconds	USL: 10 seconds (A 95% confidence/95% probability content upper tolerance limit is (b) (4))				(b) (4)

Batch C257398E

Analytical Property	Unit	Acceptance Criteria	Storage Condition	Time Point (Month)		
				0	1	3
Process Injection Time	Seconds	USL: 10 seconds (A 95% confidence/95% probability content upper tolerance limit is (b) (4))				(b) (4)

USL = Upper specification limit; NS = Not Scheduled

Q4: In section 3.2.P.7 you provided a 874 page document, where under Engineering Specifications, (b) (4)



(b) (4). We request that you scrutinize the engineering specifications provided in your submission to ensure that you provide accurate/correct device information.

Lilly Response to Question 4

To clarify, Section 3 of the 874 page document, “Supporting Document – Delivery Device Information”, contains representative documents from the Lilly Quality System to illustrate how the Combination Product GMP regulation (21 CFR 4) is applied to the prefilled syringe (PFS) and auto-injector. (b) (4)

Design Verification and Design Validation Studies. This information is an illustrative example and was not intended to represent the engineering specifications set for the submitted prefilled syringe and auto-injector delivery devices.

The results from the applicable performance tests for the delivery devices are included in the “Supporting Document – Delivery Device Information” included in Section 3.2.P.7 of the BLA. See Section 1.4 for the Prefilled Syringe (PFS) performance data and Section 2.4 for the Auto-injector performance data.

CDRH Review Comment: Performance testing specification as detailed in Sections 1.4 and 2.4 are adequate for the PFS and AI , respectively. These specification are incorporated above in memo for performance testing section.

Recommendation: Eli Lilly has provided adequate device performance data for the PFS and AI constituent of the combination product to show that the device can deliver accurate volume of the drug under the specified injection time (labeling specified 10seconds, (b) (4)). The sponsor provided adequate responses to the device deficiencies. No further device issues.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Lana Shiu, M.D.  Digitally signed by Lana L. Shiu - S Date: 2015.10.29 15:48:07 -04'00'
Branch Chief Sign-Off	 Richard C. Chapman -S 2015.10.30 09:09:09 -04'00'

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

/s/

J P PHILLIPS

11/03/2015

CDER RPM signing into DARRTS on behalf of CDRH reviewer Lana Shiu, MD because CDRH does not have access to DARRTS. Dr. Shiu electronically signed the PDF on 10/29/2015.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing and Quality
Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

Date: October 7, 2015
To: Jane Liedtka, MD
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FEI: 1819470; Establishment DUNS Number: 006421325

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Form FDA 356h – Manufacturer & Responsibilities with Contact Name:
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2. Eli Lilly S.A. – Irish Branch
Dunderrow, Kinsale
County Cork, Ireland, 99999
FEI: 3002806888; Establishment DUNS Number: 986500023

3.



4. (b) (4)
5.
6.
7.
8.
9.

Application # BLA 125521
Product Name: Ixekizumab, solution for injection, 80mg/1 mL
Proprietary Name: TALTZ™
Intended Use: This monoclonal antibody solution for injection comes in either a pre-filled syringe or an autoinjector. The product is intended to treat adult patients with psoriasis.
Consult Instructions: On 3/23/2015 CDER received a marketing application (BLA 125521) for ixekizumab 80 mg/mL with two delivery systems: prefilled syringe (PFS) and autoinjector (AI). DDDP requests a determination by CDRH/OC as to whether a device related inspection is required.

Background:

The consult request (ICC1500182) is from CDER/DDDP to provide an input on the BLA 125521, TALTZ™, Ixekizumab, solution for injection, 80mg/1 mL medical device constituents of the combination product. The Ixekizumab, solution for injection, 80mg/1 mL is composed of Ixekizumab 80mg/1 mL in glass (b) (4) syringe (b) (4)
(b) (4) assembly to create a finished PFS. The drug product remains exclusively in the glass primary container closure ((b) (4) syringe, (b) (4)) and does not contact the PFS, i.e., autoinjector. In addition to facility inspection review, documentation review of the combination product is performed. CDER had previously communicated the relevant CDRH deficiencies, Questions 5 and 6 to the applicant. Review of the applicant's response to the IR Questions 5 and 6 shows compliance to the QS call outs of the 21 CFR Part 4. Recommendation: BLA 125521 Approvable.

Manufacturing Facility Review

Firm, FEI	Responsibility	Inspection history, FACTS, TURBO	Review Comment
<p>Lilly Corporate Center Indianapolis, IN 46285, US FEI: 1819470</p>	<p>Applicant. Drug substance manufacture and storage, Release and stability testing, Storage of the master and working cell banks, Drug product manufacture, Device assembly, packaging and labeling, Release and stability testing except potency</p>	<p>Inspected: 2/2-11/2015 NAI. Routine combination risk evaluation mitigation strategy (REMS) inspection and post-marketing adverse drug experience (PADE) inspection reported under FACTS assignment number (b) (4), and focused on both the Forteo and Axiron products. The firm's previous REMS inspection was on 2/11/13 and resulted in the issuance of a single item 483 for deficiencies regarding the accuracy of the firm's REMS system as it relates to the listing of certified pharmacies and health-care facilities. Correction to this observation was verified during the current inspection. The firm's previous PADE inspection was performed on 12/12/12 and resulted in the issuance of a 2 item 483 for the firm's failure to report all adverse drug experiences that are both serious and unexpected to FDA within 15 calendar days of receipt and to submit all follow-up information on adverse drug experience reports to FDA within required timelines. Corrections to these observations were verified during the current inspection. No inspectional observations were issued during the current</p>	<p>In the last inspection, the device constituent part of ixekizumab Prefilled syringe (PFS) manufacturing and assembly was not covered. CDRH recommends that in the next inspection, this facility be considered for device inspection with particular attention to Design control and non-conforming PFS. This facility has the capability of Adverse Event and Product Complaint Reports Procedures and CAPA which can be leveraged for QS reviews.</p>

		inspection.	
Eli Lilly S.A. – Irish Branch, Dunderrow, Kinsale, County Cork, Ireland, 99999 FEI: 3002806888	Drug product potency release and stability testing	Inspection: 12/19-19/2015. VAI. Pre-approval inspection of the drug substance, ramucirumab manufacturing and related laboratory activities	Review recommendation defer to CDER
			(b) (4) Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER

Combination Product Description:

The ixekizumab PFS combination product consists of a device constituent part and a drug constituent part. The device constituent part consists of the components added to the drug container to create the delivery device. The drug constituent part is the ixekizumab formulation in its primary container.

2.3.P.2.1 Components of the Drug Product

Ixekizumab solution for injection (also referred to as ixekizumab injection), is a clear to opalescent, colorless to slightly yellow (b) (4) sterile, (b) (4) parenteral solution for subcutaneous administration. Ixekizumab injection, 80 mg/1 mL, is supplied as a sterile solution in a 1 mL glass syringe, intended for single use. The commercial drug product formulation contains the active pharmaceutical ingredient, ixekizumab, in a matrix consisting of the inactive ingredients (b) (4) sodium chloride, polysorbate 80, and Water for Injection. The complete list of ingredients and quantitative composition on a per-unit basis for the ixekizumab drug product is provided in Table 2.3.P.1-1. Each syringe is filled to enable delivery of 1 mL.

Table 2.3.P.1-1 Composition of Ixekizumab Injection, 80 mg/1 mL

Ingredient	Quantity (mg/mL)	Function	Reference to Standards
Active Ingredient			
Ixekizumab	80	Active Ingredient	Internal Standard: See Section 2.3.S.4.1, Specifications
Other Ingredients			
Sodium Citrate Dihydrate	5.11	(b) (4)	USP, Ph.Eur., JP
Citric Acid Anhydrous	0.51		USP, Ph.Eur., JP
Sodium Chloride	11.69		USP, Ph.Eur., JP
Polysorbate 80	0.30		USP, Ph.Eur., JP
Water for Injection	(b) (4)		USP, Ph.Eur., JP

2.3.P.2.2.1 Formulation Development

Three ixekizumab formulations were utilized throughout the clinical development program (b) (4) the following compositions:



- Solution Formulation (Phase 3 and limited Phase 2): 80 mg ixekizumab in 5.1 mg sodium citrate dihydrate, 0.51 mg citric acid anhydrous, (b) (4) mg sodium chloride, and 0.30 mg polysorbate 80 per mL.

The Phase 1 clinical trials were conducted using (b) (4) while Phase 2 clinical studies were conducted using (b) (4). The Phase 3 and Phase 2 (limited use) studies were conducted using a solution formulation, 80 mg. The ixekizumab for injection, (b) (4) drug product were developed based on preformulation and early phase clinical development formulation design studies. The (b) (4) drug products were supplied in a Type I glass container with an (b) (4) closure. Firm indicates stability of the DP at 2-8 C for at least 24 months. (b) (4)

The ixekizumab solution formulation was developed and optimized based on preformulation studies, pharmaceutical development experience and statistical Design of Experiments (DOE) studies. The ixekizumab injection was supplied as an 80 mg/mL solution drug product in a 1 mL glass (b) (4) syringe (b) (4) assembled into a delivery device for subcutaneous administration.

To support the transition from the (b) (4) drug product vial to the (b) (4) syringe container closure system, the component characteristics pertinent to the (b) (4) syringe system, (b) (4), needle shield and plunger were characterized and evaluated to ensure compatibility with ixekizumab, in Section 3.2.P.2.4, Container Closure System.

3.2.P.7.1 Primary container closure system Description

The primary container closure system for ixekizumab injection is a 1 mL-long clear glass syringe barrel with small round flange, 27G (b) (4) 1/2" staked needle, and closed with a (b) (4) plunger and rigid needle shield, Figure 3.2.P.7.1-1.

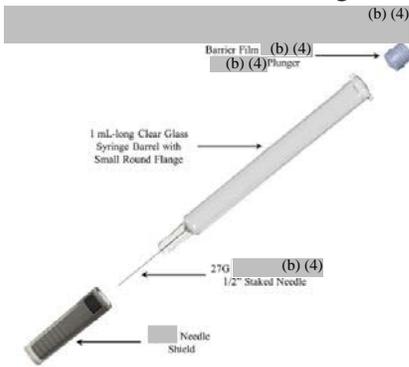


Figure 3.2.P.7.1-1 Primary Container Closure System

Table 3.2.P.7.2-1 Container Closure System Identification for Ixekizumab Injection, 80 mg/1 mL

Component	Description
Syringe Barrel	(b) (4) type I clear glass 1 mL-long syringe barrel with small round flange, 27G (b) (4) 1/2" staked needle, and (b) (4) needle shield
Plunger	(b) (4) (b) (4) plunger

3.2.P.7.3 Container Closure System Component Supplier Information

The syringe barrel and plunger are received ready-to-use from the suppliers. Component supplier information is provided in Table 3.2.P.7.3-1. Letters of Authorization for the DMFs described in Table 3.2.P.7.3-1 are provided in Module 1, Section 1.4.2. These letters give FDA permission to reference supplier drug master files on behalf of Eli Lilly and Company.

Table 3.2.P.7.3-1 Container Closure System Component Supplier Information

Component/Process	Supplier	Drug / Device Master File Number
Syringe Barrel	(b) (4)	(b) (4)
Needle Shield (b) (4)	(b) (4)	(b) (4)
Plunger	(b) (4)	(b) (4)

3.2.P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)



Table 3.2.P.5.1-1 Specifications for Ixekizumab (b) (4) Syringes

Test	Analytical Procedure	Acceptance Criteria	
		Release	End of Shelf-life
Identification Test			
Identity	(b) (4)	Conforms to the ixekizumab reference standard.	--
Identity	Cell-Based Bioassay	Conforms to the ixekizumab reference standard.	--
Quantity Test			
Quantity	UV	Not less than (b) (4) and not more than (b) (4) the label claim (equivalent to not less than (b) (4) and not more than (b) (4))	Not less than (b) (4) and not more than (b) (4) the label claim (equivalent to not less than (b) (4) and not more than (b) (4))
Potency Test			
Potency	Cell-Based Bioassay	Not less than 75% and not more than 130% potency relative to the potency of ixekizumab reference standard	Not less than 75% and not more than 130% potency relative to the potency of ixekizumab reference standard
Purity Tests			
Purity (b) (4)	SEC	Not less than (b) (4) Not more than (b) (4)	Not less than (b) (4) Not more than (b) (4)
Total Aggregates	(b) (4)	Not less than (b) (4) Not more than (b) (4)	Not less than (b) (4) Not more than (b) (4)
Purity (b) (4)	CE-SDS	Not less than (b) (4) Not more than (b) (4)	Not less than (b) (4) Not more than (b) (4)
Purity (b) (4)	CE-SDS	Not less than (b) (4) Not more than (b) (4)	Not less than (b) (4) Not more than (b) (4)

Table 3.2.P.5.1-1 (continued) Specifications for Ixekizumab (b) (4) Syringes

Test	Analytical Procedure	Acceptance Criteria	
		Release	End of Shelf-life
Other Tests			
Description	Visual	Clear to opalescent, colorless to slightly yellow (b) (4)	Clear to opalescent, colorless to slightly yellow (b) (4)
Charge Heterogeneity	(b) (4)	(b) (4)	(b) (4)
Main Peak	(b) (4)	Not less than (b) (4) and not more than (b) (4)	Not less than (b) (4) and not more than (b) (4)
Total Acidic Variants	(b) (4)	Not less than (b) (4) and not more than (b) (4)	Not less than (b) (4) and not more than (b) (4)
Total Basic Variants	(b) (4)	Not less than (b) (4) and not more than (b) (4)	Not less than (b) (4) and not more than (b) (4)
Polysorbate 80:	HPLC-UV	--*	Not less than (b) (4)
Bacterial Endotoxins (b) (4)	USP <85>	Not more than (b) (4) EU/mg	--
Particulate Matter	(b) (4)	(b) (4)	(b) (4)
Particulates (b) (4)	USP <788>	Not more than (b) (4) part/container	Not more than (b) (4) part/container
Particulates (b) (4)	(b) (4)	Not more than (b) (4) part/container	Not more than (b) (4) part/container
Sterility	USP <71>	Meets USP <71> requirements	Meets USP <71> requirements
pH	USP <791>	Not less than (b) (4) and not more than (b) (4)	Not less than (b) (4) and not more than (b) (4)

Table 3.2.P.5.1-2 Specifications for Ixekizumab Pre-Filled Syringe

Test	Analytical Procedure	Acceptance Criteria
Identity	(b) (4)	Conforms to the ixekizumab reference standard
Dose Accuracy	Volume by weight	A 95% confidence/95% probability content tolerance interval is (b) (4)
Visual/Functional Inspection	Manual Inspection	Pass

Ixekizumab Prefilled Syringe: The ixekizumab Prefilled Syringe (PFS) was developed and designed according to Design Controls described in 21 CFR 820.30, Quality System Regulation, at Eli Lilly and Company, Pharmaceutical Delivery Systems (PDS), Indianapolis, Indiana. References to the procedures and standards followed during the design, development and manufacturing of the PFS are provided in Section 2.3.P.7 Medical Device - Auto-injector.

The sterilized syringe system is a 1-mL glass syringe with a staked needle, used as the container closure system for ixekizumab (b) (4) and is indicated to comply with the requirements of ISO 11040-4 and ISO 7864. The proposed commercial version of the prefilled syringe is shown in Section 3.2.P.7, Medical Device – Prefilled Syringe.

The external components of the PFS consisting of the plunger rod, finger grips, flange cap, syringe body (casing around the syringe barrel), needle cap and cap insert components are designed for use with Lilly parenteral drug products that are filled in a 1-mL, long glass syringe with a staked needle. The (b) (4) is enclosed within the PFS parts and the parts of the PFS do not contact the drug product. The combined (b) (4) and the PFS parts form a prefilled, single-use injection device that delivers the fixed dose of drug product to the subcutaneous tissue. The length of the needle on the (b) (4) is commonly used for approved syringes for subcutaneous delivery.

The materials used to surround the (b) (4) syringe are (b) (4) parts (b) (4) (b) (4) that have been selected for their particular physical properties. These exterior materials do not contact the drug product. In the future, materials that meet these selection criteria and

do not adversely impact ISO requirements may be used. Also should any material changes be made in the future, the applicable requirements of design control including appropriate validation will be followed prior to implementation. Material properties and data sheets, manufacturing processes, shelf-life storage conditions and in-use conditions, component design, and system design were assessed to ensure the shelf life of the PFS exceeds the dating of ixekizumab.



To use the PFS, the needle cap is removed and discarded and the user inserts the needle in the skin. The needle insertion depth is controlled by the user. The plunger rod is depressed until all the fluid is injected. The movement of the plunger expels the fixed dose volume that is defined by the fill volume of the drug container. The user then removes the needle from the skin and disposes the PFS in a sharps container.

Activation of autoinjector, verbatim: The activation end of the auto-injector incorporates a lock feature, the Lock Ring, to prevent unintentional activation and an Injection Button to start the injection sequence. The injection end incorporates a Base Cap for needle shield removal and a Clear Base for stable positioning at the injection site.

The user activates the device by pressing the Injection Button to initiate the injection cycle. Pressing the Injection Button generates an audible and tactile click and the device automatically

inserts the needle, injects the drug product and following a delay to ensure that the entire contents of the syringe are delivered, retracts the needle.

The user must hold the device against the skin during the injection cycle but is not required to maintain pressure on the Injection Button. The device generates an audible and tactile click at the end of the needle retraction process. The device locks the retracted needle in place for disposal of the used auto-injector in a sharps container.

Table 3.2.P.5.1-3 Specifications for Ixekizumab Auto-Injector

Test	Analytical Procedure	Acceptance Criteria
Identity	(b) (4)	Conforms to the ixekizumab reference standard
Dose Accuracy	Volume by weight	A 95% confidence/95% probability content tolerance interval is (b) (4)
Visual/Functional Inspection	Manual Inspection	Pass
Injection Process Time	Activation to retraction timing	A 95% confidence/95% probability content upper tolerance limit (b) (4)

Drug and Device Compatibility

The exterior components of the ixekizumab PFS do not contact the drug product. The drug product remains in the primary container closure (b) (4) syringe) when assembled in the PFS. The fluid path of the drug product into the body is through the staked sterile needle in the single-use system.

The device constituent part of the combination product is classified as a surface-contacting device in contact with intact skin.

Assembly Process

The PFS is manufactured (b) (4)

(b) (4)

(b) (4) A description of the assembly process is provided in Section 3.2.P.7, Medical Device – Prefilled Syringe.

Assembly Process Validation

Process Failure Mode and Effect Analyses (pFMEA) was performed for the assembly line to define a risk based approach to process qualification and validation. The PFS assembly process validation strategy included the following:

- 1) A total of three (3) process validation batches.
- 2) Statistically-based sampling plans to provide understanding of the defect level across several assembly conditions.
- 3) Additional design verification testing to verify that the assembly process did not impact the functional performance of the PFS.
- 4) Analytical drug product testing on finished PFS to verify the assembly process did not impact the drug product quality.

Process validation data also considered meeting acceptance criteria; intactness of DP quality due to the assembly process, including container closure integrity, verification that the control

strategy is adequate to control routine batch release with consistent and reproducible yield for quality requirements.

Quality System Management of the Control Strategy

The control strategy is maintained throughout the product lifecycle via the internal quality system including deviation management, change management and periodic reviews. These quality system elements ensure that the manufacturing control strategy (including critical and non-critical controls) is maintained throughout the product lifecycle to ensure product quality and compliance with regulatory documentation.

2.3.P.3.5.2 Sterilization Process and Validation Summary

The sterility of ixekizumab (b) (4) syringes is assured through a series of controls, (b) (4)

(b) (4) A comprehensive quality assurance risk management program has been established in which risk assessments are conducted to document the prevention and detection controls.

Review Comment: (b) (4)

(b) (4)

(b) (4) It appears that the medical device aspects of the ixekizumab auto-injector were developed and designed according to Design Controls described in 21 CFR 820.30, Quality System Regulation, at Eli Lilly and Company, Pharmaceutical Delivery Systems (PDS), Indianapolis, Indiana. The firm indicates that possible changes may be made to the PFS materials. In the IR Response to Question 6, the firm acknowledged that any changes to the combination product done during development or post launch are subject to design controls (21 CFR 820.30).

CDRH Review of IR Response FDA Questions:

5. You indicate that the exterior components of the ixekizumab prefilled Syringe (PFS) is manufactured (b) (4) to (b) (4) to create a finished PFS. The drug product remains exclusively in the glass primary container closure ((b) (4) and does not contact the PFS, i.e., autoinjector. You state the device (b) (4) is a Class II medical device and indicate that the medical device aspects of the ixekizumab auto-injector were developed and designed according to Design Controls described in 21 CFR 820.30, Quality System Regulation, at Eli Lilly and Company, Pharmaceutical Delivery Systems (PDS), Indianapolis, Indiana. In the submission limited information related to ixekizumab prefilled Syringe (PFS) associated with 21 CFR 820.30 is provided. Please provide detailed summary for the Design Control per 21 CFR 820.30 as it relates to ixekizumab prefilled Syringe (PFS).

Firm's response:

The firm provided additional information in the May 5, 2015 IR Response to FDA Question 5, as stated above. The firm provided the Tables 1.1-1 and 2.1-1 Design Control Information in "Supporting Document – Delivery Device Information" submitted in 3.2.P.7 of the BLA. This provides details on how the design control is applied to the prefilled syringe (PFS) and the auto-injector, respectively. The firm indicates that the (b) (4) components and the design of the PFS were developed under the same Design Control (21 CFR 820.30) and with the same Quality System used for the auto-injector as noted in Section 1.1 of the Supporting Document. Selection criteria and testing of the components of the primary container, i.e., the (b) (4) syringe (b) (4), are described in Section 3.2.P.2.4 of the submission document. To form the PFS, the (b) (4) is assembled with the (b) (4) components shown in Figure 1.5-1 of the Supporting Document

(b) (4)

(b) (4) The PFS and auto-injector materials do not contact the drug product contained in the (b) (4).

Reviewer's comment: Firm's response provided in to CDRH Deficiency 5, is deemed to be adequate.

6. In BLA 125521 you state: In the future, materials that meet these selection criteria and do not adversely impact ISO requirements may be used. Please be informed that although changes to the medical device constituents can be made during the phase 3 with appropriate qualifications, relevant information and specifications to confirm that the combination product did not change in regards to final specifications should be provided to FDA for review. Please be advised that any changes to the combination product done during the phase are subject to design controls (21 CFR 820.30).

In addition, please provide the following summaries for FDA desk reviews.

- a. Complete information regarding compliance with 21 CFR 820.20, Management Controls
- b. Purchasing Controls as per 21 CFR 820.50
- c. Corrective and Preventive Action as per 21 CFR 820.100. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.
- d. Facilities responsible for developing the design specifications of the device constituent part and maintenance of the design history file.

Please refer to suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations, available in the guidance document "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

Firm's response:

Lilly acknowledged that any changes to the combination product done during development or post launch are subject to design controls (21 CFR 820.30). The firm cited information provided

in the “Supporting Document – Delivery Device Information” in 3.2.P.7 of the BLA represents the commercial prefilled syringe and commercial auto-injector.

The firm indicated that, should any material changes be made in the future, the requirements of design control including appropriate validation, will be followed prior to implementation (see also Tables 1.1-1 and 2.1-1 Design Control Information, which detail how design control is applied to the prefilled syringe and the auto-injector), as stated in Sections 1.3.2 and 2.3.2 of the Supporting Document.

Requested summary information is being provided as follows:

- a. Summary information regarding compliance with 21 CFR 820.20, Management Controls, is included in Section 3, Application of 21 CFR 4 of the Supporting Document. This information is located in PDS-SOP-PDS9000 Pharmaceutical Delivery Systems Quality Manual, Sections 1 – 6, and 001-003561 Parenteral Site Quality Manual, Sections 1 – 6. In addition to the information already submitted, Lilly has included in this information request response, procedure PDS-SOP-PDS4203 Management Reviews of Quality Management Systems, Document Number: PDS-SOP-PDS4203 Version 8, which provides guidance for a periodic management review of the Quality Management System for suitability, adequacy, and effectiveness.
- b. Summary information regarding Purchasing Controls as per 21 CFR 820.50 is included in Section 3, Application of 21 CFR 4 of the Supporting Document. This information is located in PDS-SOP-PDS9000 Pharmaceutical Delivery Systems Quality Manual, Section 7.4.1. The detailed procedure for the manufacturing site of the combination product is 001-006077 Material Supplier and GMP Service Provider Management. In addition to the information already submitted, Lilly has included in this information request response procedure, PDS-SOP-PDS0019 Purchasing Controls and Supplier Management, Document Number: PDS-SOP-PDS0019 Version 24, which describes the quality management requirements and responsibilities for purchasing GMP items, GMP consulting, and GMP services, including the selection and control of suppliers.
- c. Summary information regarding Corrective and Preventive Action as per 21 CFR 820.100 is included in Section 3, Application of 21 CFR 4 of the Supporting Document. This information is located in PDS-SOP-PDS9000 Pharmaceutical Delivery Systems Quality Manual, Section 8. The detailed procedure for the manufacturing site of the combination product is 001-001147 Managing Events, Non-Conformances, and Complaint RCA Investigations. In addition to the information already submitted, Lilly has included in this information request response, procedure PDS-SOP-PDS4193 Event and CAPA Management, Document Number: PDS-SOP-PDS4193 Version 12, which defines the process for managing events and the identification and implementation of corrective and preventive actions (CAPA).
- d. The facility responsible for developing the design specifications of the device constituent parts and maintenance of the design history file for the ixekizumab prefilled syringe and ixekizumab auto-injector combination products is listed below:

Eli Lilly and Company, Pharmaceutical Delivery Systems
Lilly Corporate Center
Indianapolis, IN 46285

Registration Number: 3006327424

Reviewer's comment: Firm's response provided in to CDRH Deficiency 5, is deemed to be adequate.

Deficiencies to be conveyed to the applicant

None

CDRH Office of Compliance Recommendation

The Office of Compliance (OC) at CDRH has completed the evaluation of application BLA 125521 and has the following recommendations:

1. CDRH, OC recommends BLA 125521 filable.
2. CDRH, OC recommends that in the next inspection, this facility be considered for device inspection.
3. Application BLA 125521 approvable.

**Rakhi M.
Panguluri -S**

Digitally signed by Rakhi M.
Panguluri -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130020
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Date: 2015.10.08 17:23:08 -0400'

Rakhi Dalal, Ph.D.

Prepared: RDalal: 10/7/2015
Reviewed: FVicenty:

CTS No.: ICC1500182
BLA 125521

APPEARS THIS WAY ON ORIGINAL

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

/s/

J P PHILLIPS

10/16/2015

The CDER RPM is signing this consult review into DARRTS on behalf of Rakhi Dalal (CDRH reviewer) since CDRH does not have access to DARRTS. Dr. Dalal signed this review on 10/8/2015 and her electronic signature is reflected in the PDF document.

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)**

Epidemiology: Review of Clinical Trial Data

Date: October 15, 2015

Reviewer(s): Gabriella Anic, PhD, MPH, Epidemiologist
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Division of Epidemiology 1

Subject: Risk of suicide behavior in patients treated with
ixekizumab

Drug Name(s): Taltz (ixekizumab)

Application Type/Number: BLA 125521

Applicant/sponsor: Eli Lilly

OSE RCM #: 2015-1731

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EXECUTIVE SUMMARY

The purpose of this review is for the Division of Epidemiology I (DEPI) to evaluate results from a retrospective analysis of suicide behavior and ideation in ixekizumab clinical studies and to summarize available information on suicide rates in psoriasis patients treated with biologics in clinical trials for the Division of Dermatology and Dental Products (DDDP) to determine regulatory actions on the pending biologics license application (BLA). Ixekizumab is an interleukin-17A monoclonal antibody that is currently being reviewed by DDDP for the indication of moderate to severe plaque psoriasis in adults. Recently, safety monitoring identified suicidal ideation and behavior as adverse events in the clinical trials for brodalumab, another IL-17 biologic. Subsequently, DDDP has decided to look for potential suicide safety signals for ixekizumab and requested that the sponsor conduct a retrospective analysis of the ixekizumab clinical trials data using the Columbia Classification Algorithm of Suicide Assessment (C-CASA).

In the C-CASA analysis that included 4,209 ixekizumab treated patients, nine patients experienced suicide attempts during treatment (a rate of 0.14 per 100 patients-years), and one patient made a suicide attempt after treatment. No cases of completed suicides or suicide ideation were reported. There was an imbalance between the ixekizumab and placebo groups, with all suicide behavior occurring in the ixekizumab treated subjects and none in the placebo group. The overall rate of suicide behavior (attempted and completed) for ixekizumab was the same as what was observed in brodalumab treated patients (0.14 per 100 patient-years). However, a key difference is that no completed suicides occurred for ixekizumab, whereas almost half of the suicide behavior events in brodalumab treated patients were completed suicides.

An evaluation of the rate of suicidality in clinical trials of other biologics for moderate to severe psoriasis was also conducted by DEPI. Suicidal behavior (attempts and completed combined) were highest for infliximab (0.24 per 100 patient-years) and apremilast (0.20 per 100 patient-years), a non-biologic for psoriasis that lists depression and suicidal thoughts in the Warning and Precautions section of the label. After omitting brodalumab and apremilast (due to their known suicide and depression safety signals), the pooled incidence rate of suicidality for all other psoriasis biologics was 0.04 per 100 patient-years, much lower than the incidence rate observed for ixekizumab.

Given the lack of prospective screening for suicidality and the fact that ixekizumab clinical trials were not focused on psychiatric endpoints, the incidence of suicidality may have been underestimated. The lack of any suicide ideation for ixekizumab suggests incomplete ascertainment of suicidal events since one would expect the rate of suicidal ideation to be higher than the rate of suicide attempts. The C-CASA analysis also failed to provide the total number of subjects and follow-up person-time for the placebo and etanercept active-comparator groups. Without this information it was not possible to calculate incidence rate ratios that compared all ixekizumab treated patients to all subjects who did not receive treatment.

In conclusion, data from the retrospective C-CASA analysis of ixekizumab and rates of suicidality in clinical studies of other psoriasis biologics, suggest a possible suicide safety

signal for ixekizumab. Although the rate of suicidal behavior for ixekizumab was similar to the observed rate for brodalumab, and higher than the observed rates for most other psoriasis biologics, there were no completed suicides. Based on these findings, DEPI recommends that DDDP consider the potential safety signal for suicidal behavior in their decisions about safety related PMRs and post-marketing safety surveillance for ixekizumab.

1 INTRODUCTION

1.1 BACKGROUND

The purpose of this review is to evaluate a retrospective analysis of suicide ideation and behavior in clinical study data for ixekizumab and to provide available data on the rates of suicidal behavior in psoriasis patients in clinical trials. This review was requested by the Division of Dermatology and Dental Products (DDDP) as part of their review of BLA 125521 for ixekizumab for the treatment of moderate to severe plaque psoriasis in adults. Ixekizumab is a monoclonal antibody that binds to interleukin-17A (IL-17A), a pro-inflammatory cytokine. The IL-17A ligand plays a major role in the excess keratinocyte proliferation and activation that occurs in psoriasis. Ixekizumab inhibits these actions by neutralizing IL-17A. The recommended dose is 160 mg by subcutaneous injection (two 80-mg injections) at Week 0, followed by an 80-mg injection at Weeks 2, 4, 6, 8, 10, and 12, and then 80 mg every 4 weeks.

Multiple observational studies have reported that psoriasis patients have a higher rate of psychiatric disorders including anxiety, depression, and suicidality (1-7). A population-based cohort study that used data from patient's electronic medical records in the General Practice Research Database, found the risk of suicidality (defined as diagnosis of suicidal ideation, suicide attempt, or suicide) was significantly higher in psoriasis patients compared to patients without psoriasis (hazard ratio = 1.44, 95% confidence interval = 1.32-1.57) (6). The same study estimated that psoriasis patients had a suicidality rate of 0.09 per 100 person-years. An analysis using data from the National Health and Nutrition Examination Survey, a study representative of the general US population, also found that a history of psoriasis was significantly associated with a higher risk of major depression (odds ratio = 2.09, 95% confidence interval = 1.41-3.11) (7).

Recently, clinical trials data for brodalumab, another IL-17 monoclonal antibody, suggested an increased risk of suicide among patients taking that biologic. In early 2014, safety monitoring identified suicidal ideation and behavior as adverse events of concern in the brodalumab clinical trials. Soon after, risk-mitigation strategies were implemented including implementation of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and the Patient Health Questionnaire-8 (PHQ-8), to monitor subjects for depression and suicidality in all ongoing brodalumab studies, for all indications. Patients who were observed to have suicidal ideation or behavior were referred to a mental health professional and/or discontinued from the investigational product. The biologic mechanism by which brodalumab may increase the risk of suicide is unknown.

Based on the recent findings of an increased risk for suicide in patients receiving brodalumab, DDDP examined safety data for ixekizumab for any potential signal related to suicidality. Subsequently, Eli Lilly was asked by DDDP to conduct a retrospective

analysis for suicide related events in the ixekizumab trials data using the Columbia Classification Algorithm of Suicide Assessment (C-CASA). This review will evaluate the findings of that retrospective analysis as well as summarize available clinical trial data of suicide behavior risk in psoriasis patients treated with other biologics. Findings from the review will be used to aid DDDP and the Division of Risk Management (DRISK) in determining whether a PMR study or REMS related to suicidal ideation and behavior will be required for ixekizumab.

1.2 REGULATORY HISTORY

The following is the relevant regulatory history with regard to the suicide safety concern for IL-17 biologics used to treat psoriasis:

- March 16, 2015: FDA requests a meeting with Amgen to discuss the potential risk of suicide ideation and behavior in the brodalumab development program.
- March 23, 2015: Eli Lilly submits BLA 125521 for Taltz (ixekizumab) for the indication of moderate to severe psoriasis.
- May 13, 2015: FDA meets with Amgen for brodalumab to discuss the suicidality signal observed in the clinical trial data. In response to this meeting, Amgen decides not to submit the BLA for brodalumab.
- June 24, 2015: FDA sends an IR letter to Eli Lilly requesting the following analysis:

Conduct retrospective evaluation of suicidal ideation and behavior using the Columbia Classification Algorithm of Suicide Assessment (C-CASA) for all subjects exposed to ixekizumab, regardless of indication, or identify the location of such analyses in the BLA.

- July 31, 2015: DEPI is consulted to review the results of the sponsor's retrospective evaluation of suicidality in the clinical study data:
Please provide an epidemiological perspective on the data available for the risk of suicide/suicide attempt for ixekizumab. We seek a global evaluation of the suicidal ideation and suicide attempt data, in a similar manner to what was done for brodalumab ((b) (4)), including comparison with available information on the rates of these conditions in patients with moderate to severe psoriasis.
- August 6, 2015: Eli Lilly submits the results of their retrospective C-CASA analysis for review.
- August 28, 2015: Eli Lilly submits additional clarifying information regarding the C-CASA analysis.

2 MATERIALS REVIEWED

- “Evaluation of Suicidal Ideation and Behavior by Columbia Classification Algorithm of Suicide Assessment (C-CASA) in Clinical Studies of Ixekizumab” submitted by Eli Lilly on June 24, 2015.

- “Brodalumab, 13 May 2015 FDA Meeting, Potential Risk of Suicide Ideation and Behavior” submitted by Amgen on April 13, 2015.
- “Adverse Event Rates in Psoriasis or Psoriatic Arthritis, Final Technical Report”, March 19, 2015. Prepared (b) (4) for Amgen. Submitted as part of the pre-BLA package by Amgen on April 13, 2015.
- Clinical trial data from other regulatory submissions for biologics and non-biologics for the treatment of moderate to severe psoriasis.

3 REVIEW RESULTS

3.1 C-CASA RETROSPECTIVE ANALYSIS FOR IXEKIZUMAB

3.1.1 Study Objective

The study objective was to evaluate the incidence of suicide ideation and behavior among all patients in the ixekizumab clinical studies.

3.1.2 Design & Setting

This study was a retrospective analysis of adverse event data from the ixekizumab clinical trial database using the C-CASA to classify whether an event was suicide-related.

3.1.3 Outcome & Exposure

The outcome of interest was possible suicide related adverse events (PSRAE). To identify PSRAEs, MedDRA preferred terms, AE terms, and all comment text fields (e.g., visit comments, summary comments, and reasons for discontinuation text field) of the clinical trial data were searched using the following text strings:

accident, attempt, cut, gas, hang, hung, injur, jump, mutilat, overdos, self damag, selfdamag, self harm, self-harm, self inflict, self-inflict, shoot, slash, suic, poison, asphyxiation, suffocation, firearm, burn, drown, gun, immolat, monoxide

Text strings identified in the search were independently reviewed by pairs of medical professionals internal to Eli Lilly who were trained in categorizing suicide-related events. Reviewers were blinded to treatment group, study segment, age, gender, race, ethnicity, height, weight, and country. In addition, pairs of medical professionals internal to Eli Lilly reviewed all SAEs in the Lilly Safety System for all ixekizumab clinical trials to determine whether any SAEs were suicide related. Each PSRAE was further categorized by C-CASA, a standardized suicidal rating system, to receive a final code for analysis, summarized in Table 1. If there was disagreement between reviewers, the categorization was discussed until they reached an agreement or was arbitrated by a third reviewer.

Table 1. C-CASA codes and definitions.

C-CASA Related Codes	Definitions
Code 1: Completed Suicide	Self-injurious behavior associated with some intent to die. Intent can be stated or inferred by the rater. Result is fatal.
Code 2: Suicide Attempt	Self-injurious behavior associated with some intent to die. Intent can be stated or inferred by the rater. No injury needed.
Code 3: Preparatory Acts Toward Imminent Suicidal Behavior	Person takes steps to injure self, but is stopped by self or other. Intent to die is either stated or inferred.
Code 4: Suicidal Ideation	
Active Thoughts About Killing Oneself	Active thoughts about killing oneself, not accompanied by preparatory behavior.
Passive Thoughts About Wanting To Be Dead	Passive thoughts about wanting to be dead.
Code 5: Self-Injurious Behavior, Intent Unknown	Self-injurious behavior when intent to die is unknown and cannot be inferred.
Code 6: Not Enough Information, Fatal	Insufficient information to classify the event; fatal.
Code 7: Self-Injurious Behavior, No Suicidal Intent	Self-injurious behavior associated with no intent to die. Behavior is intended to effect change in others or the environment, or intended to relieve distress.
Code 8: Not Self-Harm Related: Accident, Psychiatric, Medical, Out-of-Context	Unintentional injury, psychiatric symptoms only (when no evidence of any type of suicidality), medical symptoms or procedure only. Events that are out-of-context (a text string was found but the event is not related to self-harm).
Code 9: Not Enough Information, Nonfatal	Insufficient information to classify the event; nonfatal.

Abbreviation: C-CASA = Columbia Classification Algorithm of Suicide Assessment.

3.1.4 Studies Included and Sample Size

Data for this retrospective analysis came from three pivotal Phase 3 studies and one Phase 2 study that offered patients the option of participating in the long-term extension period for up to a total treatment period of 5 years. The data cutoff for the analysis was February 26, 2015. Results from the analysis were reported for five analysis sets that appear to represent different study periods (e.g., induction dosing, double-blind treatment, maintenance dosing) as described in Appendix A. Only one of the analysis sets included all of the 4,209 psoriasis patients treated with ixekizumab. It is not clear why the sponsor presented the data this way given that there is considerable overlap between analysis sets (Appendix A lists the studies included in each set). Furthermore, the data are incomplete, as the total number of cases of suicide behavior during ixekizumab treatment (n=9) are not all accounted for in the individual analysis sets. The report also failed to provide the total number of subjects and total person-time for those who received the placebo or etanercept active-comparator; therefore, the total sample size and person-time is unknown for the comparator groups.

3.1.5 Statistical Analyses

The analysis was limited to events that occurred during the defined treatment period and did not include events that occurred prior to the first dose of treatment or after discontinuing the defined treatment period. Incidence rates per 100 patient-years were used to summarize the number of events for C-CASA codes 1-6 and code 9 by treatment group. C-CASA Codes 1-4 are events considered to be suicide related. Codes 6 and 9

are events that were included in the C-CASA analysis because the subjects' file contained key text strings (e.g., burn, cut, accident) that classified them as possibly suicide related. The narratives provided by the sponsor for each of these subjects suggested that these events were unlikely to be related to self-harm and probably not attempted suicides. C-CASA Codes 7 and 8 were not included in the analysis since these captured injuries that occurred without suicidal intent or evidence of self-harm.

3.1.6 C-CASA Retrospective Analysis Results

Table 2 presents the incidence rates for the C-CASA Codes by treatment group. The results are reported for each of the five analysis sets. The first four analysis sets present data from the randomized controlled phases of the clinical trials. The “All Psoriasis Ixekizumab Exposures Integrated Analysis Set” includes all psoriasis patients treated with ixekizumab from both the controlled and uncontrolled phases of the clinical studies. Data from the uncontrolled, open label extension studies were not presented separately in the report.

No completed suicides were observed in any psoriasis patients enrolled in clinical studies of ixekizumab. However, there was an imbalance in the rate of suicide behavior between the ixekizumab treated group and the placebo/active-comparator groups. With the exception of one case of suicide ideation in the etanercept active-comparator group, all suicide behavior occurred in the ixekizumab treated group. Although psoriasis patients are known to have a higher background rate for depression than the general population, you would expect that the background rate for depression be the same for the treatment and placebo groups due to randomization. The fact that, during the placebo-controlled trial phases, all suicide behavior occurred in the treatment group, suggests an association between ixekizumab treatment and suicide behavior.

A total of nine suicide attempts were reported in psoriasis patients receiving ixekizumab, yielding an incidence rate of 0.14 per 100 patient-years. One additional suicide attempt was reported in the post-treatment follow-up period, occurring more than 2 months after the last dose of ixekizumab. Table 3, from the sponsor's report, lists for each suicide attempt, the dosage of ixekizumab received, time on the drug, and the study period information. The number of days on ixekizumab at the time of the other nine attempts ranged from 52 to 669 days. Two suicide attempts occurred in the placebo-controlled Induction Dosing Period, one occurred during the Maintenance Dosing Period, and six were reported in the open-label extension periods.

Table 2. Incidence of possible suicide related adverse events by analysis set.

C-CASA Codes	Ixekizumab	Placebo	Etanercept Active-Comparator
	N (IR)	N (IR)	N (IR)
Primary Psoriasis Placebo-Controlled Integrated Analysis Set	N = 2328	N = 791	
	PY = 534.5	PY = 180.0	
Code 1-3: Suicide behavior	2 (0.37)	0 (0)	NA
Code 4: Suicidal Ideation	0 (0)	0 (0)	NA

Code 6: Fatal, not enough information	0 (0)	0 (0)	NA
Code 9: Nonfatal, not enough information	5 (0.94)	3 (1.67)	
Secondary Psoriasis Placebo-Controlled Integrated Analysis Set	N = 2480 PY = 578.8	N = 827 PY = 188.6	
Code 1-3: Suicide behavior	2 (0.35)	0 (0)	NA
Code 4: Suicidal Ideation	0 (0)	0 (0)	NA
Code 6: Fatal, not enough information	0 (0)	0 (0)	NA
Code 9: Nonfatal, not enough information	6 (1.04)	3 (1.59)	NA
Psoriasis Placebo- and Active-Controlled Integrated Analysis Set	N = 1463 PY = 336.5	N = 360 PY = 83.2	N = 739 PY = 169.2
Code 1-3: Suicide behavior	2 (0.59)	0 (0)	0 (0)
Code 4: Suicidal Ideation	0 (0)	0 (0)	1 (0.59)
Code 6: Fatal, not enough information	0 (0)	0 (0)	0 (0)
Code 9: Nonfatal, not enough information	3 (0.89)	2 (2.40)	0 (0)
Psoriasis Maintenance Integrated Analysis Set	N = 824 PY = 627.6	N = 402 PY = 188.2	
Code 1-3: Suicide behavior	1 (0.16)	0 (0)	NA
Code 4: Suicidal Ideation	0 (0)	0 (0)	NA
Code 6: Fatal, not enough information	1 (0.16)	0 (0)	NA
Code 9: Nonfatal, not enough information	5 (0.61)	2 (1.06)	NA
All Psoriasis Ixekizumab Exposures Integrated Analysis Set	N = 4209 PY = 6479.8		
Code 1-3: Suicide behavior	9 (0.14)	NA	NA
Code 4: Suicidal Ideation	0 (0)	NA	NA
Code 6: Fatal, not enough information	2 (0.03)	NA	NA
Code 9: Nonfatal, not enough information	39 (0.60)	NA	NA

IR = incidence rate per 100 patient-years, PY = patient-years, NA = data were not available for the corresponding treatment group.

There were two AEs in the ixekizumab group that were fatal but lacked enough information to determine whether they were completed suicides (C-CASA Code 6). One of the deaths was a 52-year old male who died from unknown causes after 49 days of Maintenance Dosing (80 mg every 4 weeks). The subject called the study investigator shortly before their death complaining of stomach pain and was advised to visit their primary care physician. No autopsy information was available for this individual. The second death was a 52-year old male who may have died from a myocardial infarction after 432 days on ixekizumab (80 mg every 4 weeks) during the Long-Term Extension Period. A colleague informed the study site that the patient possibly had a heart attack

and died, however, further information including autopsy status were unknown. Medical Officers in DDDP have reviewed the clinical information for both these patients and deemed that it is unlikely that they were completed suicides.

Events classified as C-CASA Code 9 were more frequent in the placebo group. These were nonfatal events that lacked enough information to determine whether or not they were suicide related. Review of the narratives provided by the sponsor for each of these cases revealed that these events consisted of burns, minor lacerations, and motor vehicle accidents that were unlikely to be related to self-harm and therefore not informative in estimating the rate of suicidality in each group.

Table 3. Ixekizumab treatment duration and dosage for patients with suicide attempts.

Study-Patient ID	Age at Study Entry/Sex	Event Preferred Term	Study Period	Ixekizumab Treatment Group at the Time of Event	Days on Ixekizumab Treatment at the Time of the Event
RHBA-216-4612	55/female	Suicide attempt	Induction Dosing	80 mg Q4W	52
RHBA-456-6687	29/male	Suicide attempt	Induction Dosing	80 mg Q2W	71
RHBA-151-3006	39/male	Suicide attempt	Maintenance Dosing	80 mg Q12W	217
RHAJ-105-1507	69/male	Suicide attempt	Extension	120 mg Q4W	394
RHAZ-151-3001	49/female	Suicide attempt	Extension	80 mg Q4W	447
RHBC-140-2855	26/male	Suicidal ideation	Extension	80 mg Q4W	463
RHBA-486-6765	47/female	Suicide attempt	Extension	80 mg Q4W	493
RHAZ-163-3614	27/male	Suicide attempt	Extension	80 mg Q4W	614
RHAZ-452-6568	45/male	Suicide attempt	Extension	80 mg Q4W	669
RHBC-152-3058	34/female	Suicide attempt	Post-Treatment Follow-Up	—	>2 months after last dose of ixekizumab (80 mg Q4W)

Abbreviations: Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks.

3.2 INCIDENCE OF SUICIDE BEHAVIOR IN BRODALUMAB CLINICAL STUDIES

In April 2015, Amgen submitted a comprehensive overview of suicide behavior in patients treated with brodalumab, another IL-17 biologic for the treatment of psoriasis. Table 4, which was included in Amgen’s pre-BLA meeting package, presents the incidence rate of suicide behavior in the 4,464 psoriasis patients who received ≥ 1 dose of brodalumab through March 2015. The rate of suicidal behavior in brodalumab treated patients was 0.14 per 100 patient-years. There were a total of 11 events classified as suicidal behavior, including seven suicide attempts and four completed suicides. The rate of suicidal behavior for ixekizumab (0.14 per 100 patient-years) was the same as what was observed for brodalumab. The main difference between the two treatments was that almost half of the suicide behavior events in brodalumab were completed suicides, while there were no completed suicides for ixekizumab.

The time from treatment initiation to suicide event was similar for both biologics. The range of time between first active dose of brodalumab and attempted and completed suicides was 40-754 days and 97-845 days, respectively. The time from treatment

initiation to suicide attempts for ixekizumab was 52-669 days. Three of the four completed suicides for brodalumab occurred outside of the exposure period (i.e., >14 days after last active dose); those suicides occurred 19, 27, and 58 days after last active treatment. Two suicide attempts also occurred outside the exposure period at 16 and 17 days after last active dose of brodalumab. The report for ixekizumab failed to report the time since last treatment for all of the suicide attempts, however, only one patient was classified as having an event post-treatment when they attempted suicide more than 2 months after last ixekizumab treatment, implying that all other suicide attempts occurred while actively being treated with ixekizumab.

Table 4. Incidence rates per 100 patient-years of suicide behavior by MedDRA Preferred Term from first dose of brodalumab through March 2015.

Events of Interest Category Preferred Term	Brodalumab				
	210 mg Q2W After Ustekinumab (Subj-yr =602.5) (N = 567) n (r)	Subjects with Brodalumab Exposure Only			All (Subj-yr =7894.6) (N = 4464) n (r)
		Overall Variable Dosing (Subj-yr =4567.8) (N = 2327) n (r)	Overall 140 mg Q2W (Subj-yr =435.6) (N = 269) n (r)	Overall 210 mg Q2W (Subj-yr =2288.6) (N = 1301) n (r)	
Suicidal Ideation and Behavior	2 (0.33)	10 (0.22)	0 (0.00)	14 (0.61)	26 (0.33)
Complete suicide	0 (0.00)	0 (0.00)	0 (0.00)	4 (0.17)	4 (0.05)
Completed suicide	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.13)	3 (0.04)
Intentional overdose	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.01)
Suicidal behavior adverse event	0 (0.00)	4 (0.09)	0 (0.00)	7 (0.31)	11 (0.14)
Completed suicide	0 (0.00)	0 (0.00)	0 (0.00)	3 (0.13)	3 (0.04)
Suicide attempt	0 (0.00)	2 (0.04)	0 (0.00)	2 (0.09)	4 (0.05)
Intentional overdose	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.04)	1 (0.01)
Suicidal behavior	0 (0.00)	1 (0.02)	0 (0.00)	1 (0.04)	2 (0.03)
Intentional self-injury	0 (0.00)	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.01)
Suicidal ideation adverse event	2 (0.33)	8 (0.18)	0 (0.00)	8 (0.35)	18 (0.23)
Suicidal ideation	2 (0.33)	7 (0.15)	0 (0.00)	8 (0.35)	17 (0.22)
Depression suicidal	0 (0.00)	1 (0.02)	0 (0.00)	0 (0.00)	1 (0.01)

MedDRA v. 17.1; N= subjects in Studies 20090062/20090403, 20120102, 20120103, and 20120104 with ≥ 1 dose of brodalumab

3.3 RATES OF SUICIDE BEHAVIOR IN CLINICAL STUDIES OF OTHER PSORIASIS TREATMENTS

3.3.1 Data from Literature Review of Psoriasis Clinical Studies

In an effort by Amgen to provide a background rate of suicide behavior in psoriasis patients enrolled in clinical trials, (b) (4) the consultants to Amgen, conducted a systematic literature review of phase III and phase IV clinical trials of adult patients with psoriasis and/or psoriatic arthritis treated with biologic agents. Results of the literature review were submitted as part of the Amgen pre-BLA meeting package. The clinical trial data reviewed came from open-label extensions of phase III trials, phase II/III trials, and trials of unspecified phase with at least 100 subjects. The studies reviewed included patients treated with the following biologic agents: etanercept, adalimumab, infliximab, golimumab, ustekinumab, secukinumab, brodalumab, ixekizumab, and certolizumab.

Table 5 presents the incidence of suicide behavior in psoriasis patients treated with the biologics of interest in phase III or IV clinical trials. The incidence rates were reported for all studies combined and were not reported by individual biologic agents. Across 29 studies of psoriasis biologics with 21,062 total patient-years, there were four completed suicides, yielding a rate of 0.02 per 100 patient-years. “Suicide ideation or behavior” occurred at a rate of 0.02 per 100 patient-years although the report failed to specify if suicide behavior referred to suicide attempts, completed suicides or both, and the definition may have varied across studies. The incidence rate of “suicide attempts” was 0.11 per 100 patients-years.

Table 5. Incidence rates of suicidal behavior or ideation among psoriasis patients treated with biologics in phase III or IV clinical trials.

Adverse event	Total Studies	Total Events	Total Patient-Years	Events per 100 Patient-Years	95% Confidence Interval
Completed Suicide	29	4	21,062	0.02	0.01, 0.05
Suicide ideation or behavior	4	2	9,715	0.02	0.002, 0.07
Suicide attempt	3	3	2,675	0.11	0.02, 0.33

3.3.2 Data from Regulatory Submissions

To provide a comparison of data for ixekizumab to suicidal adverse event rates previously observed in patients with psoriasis, one of the reviewers (AM) surveyed data from other regulatory submissions for drugs and biologics in the treatment of psoriasis. From the sources noted in Table 6, the reviewer obtained event counts for suicide, suicide attempt, and (if available) suicidal ideation, with corresponding person-time of exposure and numbers of subjects. The emphasis was on data from psoriasis trials specifically, when the data were available, but in some submissions the sponsor pooled psoriasis trial data with data from trials for other indications. The reviewer included only the data for the compound under development, as the placebo and active comparator groups had limited sample sizes and those data were less informative. Apremilast, a non-biologic agent for the treatment of psoriasis was included because depression and suicidal thoughts are listed in the Warnings and Precautions section of the label. The reviewer calculated rates for suicide, attempted suicide, and suicidal ideation, per 100,000 person-years, without attempting to estimate statistical confidence intervals for these values. The reviewer also calculated overall pooled rates, but omitted two compounds that are probable outliers: brodalumab (because it has a signal for suicide), and apremilast (because it has a label warning for depression). It should be mentioned that the sparseness of the data (low event counts) results in imprecise rate estimates. Also, although these rates reflect mostly psoriasis trial data, there was some heterogeneity in the indications studied.

The pooled completed suicide rate of 0.02 per 100 patient-years (23.7 per 100,000 patient-years) (four suicides/21,131 patient-years of treatment with six compounds) was in line with the rate from the (b) (4) literature review (0.02 per 100 patient-years). The attempted suicide rate for ixekizumab was similar to what was reported for apremilast (0.13 per 100 patient-years or 134.9 per 100,000 patient-years) and much higher than the pooled estimate of attempted suicides for other psoriasis biologics (0.02 per 100 patient-years or 23.7 per 100,000 patient-years). Infliximab (0.24 per 100 patient-years or 237.5 per 100,000 patient-years) was the only psoriasis treatment to have a higher rate of suicide attempts than ixekizumab.

Table 6. Rates of Suicide Behavior in Clinical Trials for Psoriasis Treatments.

Dataset	N	Patient years	Completed suicides, N	Suicide attempts, N	Suicides per 100,000 PY	Suicide attempts per 100,000 PY	Suicides + suicide attempts per 100,000 PY	Suicidal ideation, N	Suicidal ideation per 100,000 PY	Adjudicated with C-CASA?
Brodalumab, all indications ¹	5,208	8,519	6**	8	70.4	93.9	164.3	19	223.0	No
Brodalumab in psoriasis trials ¹	4,464	7,895	4**	7	50.7	88.7	139.3	18	228.0	No
Apremilast in Phase 2 & 3 trials for psoriasis, psoriatic arthritis, rheumatoid arthritis ²	2,401	1,483	1	2	67.4	134.9	202.3	2	134.9	Yes
Etanercept in psoriasis trials ³	1,807	2,773	0	1	0.0	36.1	36.1	2	72.1	No
Adalimumab psoriasis OL study M03658 ⁴	1,468	4,069	1**	0	24.6	0.0	24.6	3	73.7	No
Secukinumab psoriasis and psoriatic arthritis Phase 3 trials ⁵	3,928	3,225	0*	1	0.0	31.0	31.0	1	31.0	Yes
Ustekinumab psoriasis safety 4-yr update ⁶	3,117	6,791	1	0	14.7	0.0	14.7	0	0.0	No
Infliximab psoriasis safety summary ⁷	1,564	1,263	0	3	0.0	237.5	237.5	0	0.0	No
Briakinumab in psoriasis trials ⁸	2,520	3,011	2**	0	66.4	0.0	66.4	1	33.2	No
<i>Pooled, omitting brodalumab and apremilast</i>	<i>14,404</i>	<i>21,131</i>	<i>4</i>	<i>5</i>	<i>18.9</i>	<i>23.7</i>	<i>42.6</i>	<i>7</i>	<i>33.1</i>	

PY = patient-years

1 Amgen briefing document for 5-13-2015 meeting

2 Celgene Apremilast "C-CASA White Paper"

3 Amgen Etanercept ISS for long-term exposure (12-13-2006)

4 Abbott adalimumab study report (4-14-2010)

5 Novartis secukinumab C-CASA Report

6 Centocor submission (7-6-2011)

7 Centocor submission (8-5-2005)

8 EMA Rapporteurs' Day 80 Critical Assessment Report (12-10-2010)

*One subject committed suicide during screening

**Includes suicides during post-treatment follow-u

4 DISCUSSION

Although definitive conclusions cannot be made, the imbalance of suicidal behavior between the placebo and ixekizumab treated patients in the C-CASA analysis, as well as the higher incidence of attempted suicides for ixekizumab compared to other psoriasis biologics, suggest a possible safety signal of suicidality for ixekizumab. Below are some caveats regarding the reviewed data.

The incidence of suicide behavior and ideation may be underestimated in ixekizumab treated patients. Ordinarily one would expect that the rate of suicide attempts would be considerably higher than the rate of completed suicide, and the rate of suicidal ideation to be higher still, as was seen in FDA's meta-analysis of antidepressant clinical trials (8). This pattern was not evident in the ixekizumab clinical trials which reported no cases of suicide ideation in the C-CASA analysis, suggesting incomplete ascertainment of suicidal events. However, the ratio of attempted/completed suicides for ixekizumab was in line with what is expected. Based on data from the CDC's Web-based Injury Statistics Query and Reporting System (WISQARS), it is estimated that there are 12 attempted suicides for every completed suicide. Brodalumab had an almost one to one ratio of attempted suicides to completed suicides, suggesting that additional suicide attempts went uncaptured in the brodalumab trials. In contrast, the ixekizumab results were consistent with the CDC's estimate, with 10 attempted suicides and zero completed suicides. Given that the ixekizumab clinical trials were not psychiatric studies and that there was no prospective screening for suicidality, it is possible that instances of suicide ideation or behavior may have gone unreported. The brodalumab trials did start prospectively monitoring patients for suicide behavior, however, this screening did not begin until late into the trials after most subjects had already received brodalumab for more than a year. It is also possible that patients lost to follow-up had committed suicide and were therefore not captured.

The report was missing complete information about the placebo and active comparator groups. The report failed to provide the total number of subjects and follow-up person-time for the placebo and etanercept active-comparator groups. That is, the report omitted comparator denominator data for the All Psoriasis Ixekizumab Exposures Integrated Analysis Set (see table 2 above, corresponding to Table 6.10 in the sponsor's report). Since there was overlap across the analysis sets it was not possible to pool the placebo and comparator group data in this report. Complete information about the comparator groups would allow for calculating incidence rate ratios comparing all ixekizumab treated patients to all subjects who did not receive treatment. However, it is expected that the follow-up time is shorter for the placebo group than the active treatment group, in which patients were followed for up to five years in open-label studies. Given that most of the suicide attempts in the ixekizumab treated patients occurred during the open-label extension period, it is likely that the rate of suicidal behavior would be smaller in the placebo group due to the shorter follow-up time.

5 CONCLUSION

Data from the retrospective C-CASA analysis of ixekizumab clinical trials show an imbalance in the rate of suicide behavior between patients in the ixekizumab and placebo

treatment groups. Although no completed suicides were observed for ixekizumab, 10 instances of attempted suicide occurred in the ixekizumab group and none in the placebo group. The rate of suicidality (completed and attempted suicides) was 0.14 per 100 patient-years for both ixekizumab and brodalumab. The primary difference being that almost half of the events for brodalumab were completed suicides, whereas no completed suicides occurred for ixekizumab. Ixekizumab had an appreciably higher rate of suicidal behavior compared to a pooled estimate of other psoriasis biologics (0.04 per 100 patient-years), and the same rate of suicide attempts as apremilast, a non-biologic with a label warning for depression and suicidal thoughts. It should also be noted that another psoriasis biologic, infliximab, had a higher rate of suicidality (0.24 per 100 patients-year) than both ixekizumab and brodalumab and may warrant further investigation.

6 RECOMMENDATIONS TO DDDP

To further evaluate the potential safety concern of suicidality in patients treated with ixekizumab, DEPI recommends that DDDP consider enhanced pharmacovigilance, REMs, or a possible safety PMR. Although, DEPI acknowledges that there would be many challenges to designing a PMR safety study that captures suicidality as an outcome.

7 RECOMMENDATIONS TO THE SPONSOR

The report failed to provide the total number of subjects and follow-up person-time for the placebo and etanercept active comparator groups. Send an equivalent of Table 6.10 for each comparator group with the total number of subjects and follow-up time and the total frequency of each C-CASA code.

CC:

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APPENDIX A. SUMMARY OF STUDIES INCLUDED IN THE C-CASA ANALYSIS

Analysis Set	When Used	Treatment Period	Analysis Population	Treatment Groups	Treatment Comparisons
Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, RHBC)	Initial BLA submission for Ps	Period 2 (Induction Dosing)	Ps Safety Population	<ul style="list-style-type: none"> • Pooled placebo • Pooled ixekizumab 80 mg Q4W • Pooled ixekizumab 80 mg Q2W • Pooled ixekizumab • Total 	<ul style="list-style-type: none"> • Pooled ixekizumab vs. pooled placebo • Pooled ixekizumab 80 mg Q4W vs. pooled placebo • Pooled ixekizumab 80 mg Q2W vs. pooled placebo
Secondary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAG, RHAJ, RHAZ, RHBA, RHBC)	New for this response	Period 2 (Double-Blind Treatment/Induction Dosing)	Ps Safety Population	<ul style="list-style-type: none"> • Pooled placebo • Pooled ixekizumab • Total 	<ul style="list-style-type: none"> • Pooled ixekizumab vs. pooled placebo
Psoriasis Placebo- and Active-Controlled Integrated Analysis Set (Studies RHBA, RHBC)	Initial BLA Submission for Ps	Period 2 (Induction Dosing)	Ps Safety Population	<ul style="list-style-type: none"> • Pooled placebo • Pooled etanercept • Pooled ixekizumab 80 mg Q4W • Pooled ixekizumab 80 mg Q2W • Pooled ixekizumab • Total 	<ul style="list-style-type: none"> • Pooled ixekizumab vs. pooled placebo • Pooled etanercept vs. pooled placebo • Pooled ixekizumab vs. pooled etanercept • Pooled ixekizumab 80 mg Q4W vs. pooled placebo • Pooled ixekizumab 80 mg Q2W vs. pooled placebo • Pooled ixekizumab 80 mg Q4W vs. pooled etanercept • Pooled ixekizumab 80 mg Q2W vs. pooled etanercept
RA Placebo-Controlled Integrated Analysis Set (Studies RHAF, RHAK, RHAL)	New for this response	Period 2 (Double-Blind Treatment Period)	RA Safety Population	<ul style="list-style-type: none"> • Placebo • Total ixekizumab • Total 	<ul style="list-style-type: none"> • Pooled ixekizumab vs. placebo

Analysis Set	When Used	Treatment Period	Analysis Population	Treatment Groups	Treatment Comparisons
PsA (RHAP) Placebo-Controlled Analysis Set	4-Month Safety Update for Ps BLA	Period 2 (Double-Blind Treatment Period)	PsA (RHAP) Safety Population	<ul style="list-style-type: none"> • Placebo • Adalimumab • Ixekizumab 80 mg Q4W • Ixekizumab 80 mg Q2W • Total ixekizumab • Total 	<ul style="list-style-type: none"> • Total ixekizumab vs. placebo • Adalimumab vs. placebo • Ixekizumab 80 mg Q4W vs. placebo • Ixekizumab 80 mg Q2W vs. placebo
Ps Maintenance Integrated Analysis Set (Studies RHAZ, RHBA)	Initial BLA Submission for Ps and 4-Month Safety Update for Ps BLA	Maintenance Dosing Period	Maintenance Dosing Period Primary Population	<ul style="list-style-type: none"> • Pooled placebo • Pooled ixekizumab 80 mg Q12W • Pooled ixekizumab 80 mg Q4W • Pooled ixekizumab • Total 	<ul style="list-style-type: none"> • Pooled ixekizumab vs. pooled placebo • Pooled ixekizumab 80 mg Q12W vs. pooled placebo • Pooled ixekizumab 80 mg Q4W vs. pooled placebo
All Ps Ixekizumab Exposures Integrated Analysis Set (Studies RHAG, RHAJ, RHAT, RHAZ, RHBA, RHBC, RHBL)	Initial BLA Submission for Ps and 4-Month Safety Update for Ps BLA	All treatment periods where ixekizumab is administered	All Ps Ixekizumab Exposures Safety Population	<ul style="list-style-type: none"> • Pooled ixekizumab 	<ul style="list-style-type: none"> • NA
All RA Ixekizumab Exposures Integrated Analysis Set (Studies RHAF, RHAK, RHAL, RHAM)	Initial BLA Submission for Ps	All treatment periods where ixekizumab is administered	All RA Ixekizumab Exposures Safety Population	<ul style="list-style-type: none"> • Pooled ixekizumab 	<ul style="list-style-type: none"> • NA

Abbreviations: BLA = Biologics License Application; NA = not applicable; Ps = plaque psoriasis; PsA = psoriatic arthritis; Q12W = every 12 weeks; Q2W = every 2 weeks; Q4W = every 4 weeks; RA = rheumatoid arthritis; vs. = versus

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

/s/

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10/15/2015

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Signing on behalf of Lockwood Taylor, one of the secondary reviewers

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

Drug Utilization Review

Date: October 2, 2015

Reviewer(s): Patty Greene, Pharm.D, Drug Use Data Analyst
Division of Epidemiology II (DEPI II)

Team Leader: Mohamed A. Mohamoud, Pharm.D, M.P.H., BCPS
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Deputy Division Director: CDR David Moeny, MPH, R.Ph. USPHS
Division of Epidemiology II (DEPI II)

Drug Name(s): acitretin, adalimumab, apremilast, azathioprine,
cyclosporine, etanercept, hydroxyurea, infliximab,
methotrexate, methoxsalen, mycophenolate mofetil
secukinumab, ustekinumab

Application Type/Number: Multiple

Applicant/sponsor: Multiple

OSE RCM #: 2015-1236

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EXECUTIVE SUMMARY

The Division of Dermatology and Dental Products (DDDP) is conducting a clinical review of ixekizumab, a pending biologics license application (BLA) for the treatment of adult patients with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. DDDP requested drug utilization data for systemic treatments currently used by physicians for psoriasis. In support of this request, the Division of Epidemiology II (DEPI II) examined the number of times a select group of systemic drug therapies were mentioned in association with the treatment of psoriasis (ICD-9 696.x) by querying a database of U.S. office-based physician's survey data, from January 1, 2009 to June 30, 2015, cumulative. DEPI II conducted a literature search for review articles that provided an evidence-based update on systemic therapies or phototherapy used to treat psoriasis from January 1, 2009 to August 31, 2015. We also searched the literature for descriptive studies on physician preferences for first-line therapy of moderate to severe psoriasis for the same time period.

According to a U.S. office-based physician survey, for the time period of January 1, 2009 to June 30, 2015 the top systemic drug therapies mentioned in association with the treatment of psoriasis (ICD-9 696.x) were as follows. For adults 18 years or older, etanercept and methotrexate were the most commonly reported products associated with a diagnosis of psoriasis; each accounted for 30% of the total share (1.8 million mentions each). Adalimumab and ustekinumab ranked second and third and accounted for approximately 21% (1.3 million mentions) and 8% (528,000 mentions) of the total share, respectively. Apremilast and acitretin ranked fourth, and accounted for approximately 4% of the total share (235,000 to 238,000 mentions). Infliximab ranked fifth and accounted for approximately 2% of the total share (112,000 mentions).

Cyclosporine, secukinumab, methoxsalen, and hydroxyurea accounted for 1% of the total share combined and were below the acceptable count to provide a reliable national estimate of use. Mycophenolate mofetil and azathioprine were not captured for the treatment of psoriasis from U.S. office-based physician survey for the review period.

Wan et al. (2011) assessed dermatologists' preference for first-line treatments of moderate to severe psoriasis in healthy adult patients. In this descriptive study, Wan et al. found that the most preferred treatments for moderate to severe psoriasis in healthy adults were UVB phototherapy (male 39.5%; female 56.3%), etanercept (male 15.0%; female 18.6%), methotrexate (male 15.8%; female 4.4%), and adalimumab (male 11.6%; female 9.6%).¹

Two review articles by Sandoval et al. (2014) and Herrier (2011) found favorable safety profiles for biologic agents (i.e. adalimumab, infliximab and ustekinumab) when compared to traditional immunosuppressive/immunomodulatory systemic agents (methotrexate and cyclosporine). Sandoval et al. reported methotrexate, adalimumab, etanercept, and ustekinumab as first-line treatment for moderate to severe psoriasis and acitretin as a first-line treatment for chronic palmoplantar or pustular psoriasis. For biologic agents, infliximab was recommended as a second- or third-line biologic agent.^{2,3}

Another review article by Kelly III et al. (2015) examined clinical data on oral systemic therapies used in combination with ultraviolet phototherapy or biologic therapy for the

treatment of psoriasis. Kelly III et al. found methotrexate was often used in combination with other oral systemic therapies, ultraviolet phototherapy, or biologic therapy. Cyclosporine was often used as a bridge therapy and prescribed concurrently with traditional systemic therapy (i.e. methotrexate or acitretin) or biologic therapies, then titrated down once therapeutic levels of the traditional systemic/biologic therapy are achieved. Acitretin was also used in combination with ultraviolet phototherapy and biologic therapies. Mycophenolate mofetil, hydroxyurea, and 6-thioguanine (antimetabolite of azathioprine should be used after patients have failed both oral systemic or biologic therapy.⁴

1 INTRODUCTION

The Division of Dermatology and Dental Products (DDDP) is conducting a clinical review of ixekizumab, a pending BLA for the treatment of adult patients with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. DDDP requested drug utilization data on systemic treatments currently used by physicians to treat psoriasis. In support of this request, the Division of Epidemiology II (DEPI II) examined the number of times a select group of systemic drug therapies were reported for the treatment of psoriasis (ICD-9 696.x) by querying a database of U.S. office-based physicians survey data, from January 1, 2009 to June 30, 2015, cumulative. DEPI II also conducted a literature search for review articles that provided an evidence-based update on systemic therapies or phototherapy for psoriasis from January 1, 2009 to August 31, 2015. We also searched the literature for descriptive studies on physician preferences for first-line therapy of moderate to severe psoriasis for the same time period.

1.1 PRODUCT INFORMATION¹

Generic Name	Dosage form /Strength	Indication(s)
Oral Systemic Therapy		
Acitretin	Oral capsule Strength: 10mg, 17.5mg, 22.5mg, 25mg	For the treatment of severe psoriasis in adults
Apremilast	Oral tablet Strength: 10mg, 20mg, 30mg	For the treatment of adult patient with active psoriatic arthritis
Azathioprine	Oral tablet Strength: 50mg	<ul style="list-style-type: none"> •Adjunct for the prevention of rejection in renal homotransplantations •For the treatment of active rheumatoid arthritis to reduce signs and symptoms
Cyclosporine	Oral capsule: 25mg, 50mg,	•For the prophylaxis of organ rejection in

¹ DailyMed. <http://dailymed.nlm.nih.gov/dailymed/drugInfo> Accessed September 1, 2015

	100mg, oral solution: 100mg/mL	kidney, liver, and heart allogeneic transplants. •For the treatment of patients with severe active, rheumatoid arthritis where the disease has not adequately responded to methotrexate. •For the treatment of adults, nonimmunocompromised patients with severe (i.e., extensive and/or disabling), recalcitrant, plaque psoriasis who have failed to respond to at least one systemic therapy (e.g. PUVA, retinoids, or methotrexate) or in patients whom other systemic therapies are contraindicated, or cannot be tolerated
Hydroxyurea	Oral capsule: 250mg, 500mg tablet: 1 gm	For the treatment of resistant chronic myeloid leukemia and locally advanced squamous cell carcinomas of the head and neck (excluding the lip) in combination with chemo-radiation
Methotrexate	Oral tablet: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg	•Antineoplastic chemotherapy: Treatment of gestational choriocarcinoma, chorioadenoma destruens, and hydatidiform mole. •Psoriasis: Symptomatic control of psoriasis (severe, recalcitrant, disabling). •Rheumatoid Arthritis: Management of selected adults with severe, active RA (ACR criteria); active polyarticular-course juvenile rheumatoid arthritis.
Methoxsalen	Oral capsule Strength: 10 mg	(with long wave UVA radiation) For the symptomatic control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy.
Mycophenolate mofetil	Oral capsule: 250 mg tablet: 500 mg oral suspension: 200 mg/mL	For the prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac, hepatic transplants.
Biologic Agents		
Adalimumab, Etanercept, Infliximab	Adalimumab: Pen/Vial: 40 mg/0.8mL, prefilled syringe: 10 mg/	•For reducing signs and symptoms, including major clinical response, inhibiting the progression of structural damage, and improving physical function

	0.2mL, 20 mg/0.4mL, 40 mg/0.8mL	in adults patients with moderately to severely active rheumatoid arthritis
	Etanercept: Single-use prefilled syringe, prefilled sureclick autoinjector: 50 mg/mL, vial: 25 mg	<ul style="list-style-type: none"> •For reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older •For reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adults patients with active psoriatic arthritis
	Infliximab: vial: 100 mg	<ul style="list-style-type: none"> •For reducing the signs and symptoms in adults patients with active ankylosing spondylitis •For the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate
Secukinumab	Single-use pen/prefilled syringe: 150 mg/mL, vial: 150 mg	For the treatment of moderate to severe plaque psoriasis in adults patients who are candidates for systemic therapy or phototherapy.
Ustekinumab	Single-use prefilled syringe/vials : 45 mg/0.5mL, 90 mg/mL	<ul style="list-style-type: none"> •For the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy •For the treatment of adults patients (18 years or older) with active psoriatic arthritis

2 METHODS AND MATERIAL

2.1 DATA SOURCES USED

A proprietary drug use database available to the Agency was used to conduct this analysis (see *Appendix 2* for database descriptions). ^{(b) (4)}

^{(b) (4)} was used to examine national estimates of the number of times a product

² The term "drug uses" refer to mentions of a drug in association with a diagnosis during a patient visit to an office-based physician. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

in the selected market was reported for the treatment of psoriasis (ICD-9 696.x), stratified by patient age (0-17, 18+ years) from a U.S. office-based physician survey database, January 1, 2009 to June 30, 2015, cumulative. Although the physician survey data provides insight into drug prescribing patterns associated with indication, it does not capture if a prescription was ultimately dispensed for the treatment of psoriasis. Due to the multiple indications of some products and varying settings of care where these drugs are primarily dispensed from, national estimates of prescriptions dispensed for the treatment of psoriasis are not available.

2.2 LITERATURE SEARCH

DEPI II searched PubMed for review articles that discussed treatment recommendations for systemic therapies currently used by physicians in moderate to severe psoriasis. Articles were included for further analysis that offered a comprehensive review of treatment recommendations for oral systemic or biologic therapies listed in section 1.1 (see Product Information Table).

We searched the terms (((physician preference) AND current systemic therapies for psoriasis) OR current systemic treatment for psoriasis) and found 72 review articles using a custom date range from January 1, 2009 to August 31, 2015. The search identified 64 English language articles. Search results were then manually reviewed by title and abstract and 42 review articles were excluded due to a lack of comprehensive information on psoriasis treatments. Eleven articles reviewed treatments for psoriatic or rheumatoid arthritis and were excluded. Five articles included a discussion of emerging psoriasis treatments under development and were excluded. Of the remaining 6 review articles, 2 reviews included a pharmacoeconomic analysis of psoriasis treatments and 1 review focused on medication adherence; both were excluded. We also searched PubMed for descriptive studies of physician practice patterns to determine what treatments are being used as first-/second line to treat psoriasis by searching the keywords (dermatologist preference for first line therapy of moderate to severe psoriasis). Four publications were selected; three that provided an evidence-based update on systemic therapies or phototherapy used to treat psoriasis and one descriptive study examining physician preferences for first-line therapy of moderate to severe psoriasis.

3 RESULTS

3.1 OFFICE-BASED PHYSICIAN SURVEY DATA

Table 1 displays the nationally estimated number of times a product was reported (i.e. drug use mentions) for the treatment of psoriasis (ICD-9 696.x), stratified by patient age, as reported by U.S. office-based physician surveys, January 1, 2009 to June 30, 2015, cumulative. For adults 18 years or older, etanercept and methotrexate were the most commonly reported products associated with a diagnosis of psoriasis; each accounted for 30% of the total share (1.8 million mentions each), respectively. Adalimumab and ustekinumab accounted for approximately 21% (1.3 million mentions) and 8% (528,000 mentions) of the total share, respectively. Apremilast and acitretin, each accounted for approximately 4% of the total share (235,000 mentions and 238,000 mentions), respectively. Finally, infliximab accounted for approximately 2% of the total share (112,000 mentions). Cyclosporine, secukinumab, methoxsalen, and hydroxyurea were

below the acceptable count (<100,000 mentions) to provide a reliable national estimate of use. There were no reports captured of mycophenolate mofetil or azathioprine for the treatment of psoriasis from office-based physician survey database during the review period.

For patients under 17 years of age, products reported for the treatment of psoriasis included methotrexate, adalimumab, and acitretin. However, drug use mentions were below the acceptable count to provide a reliable estimate of national use.

Table 1. Drugs associated with the treatment of Psoriasis (ICD-9 696.x), stratified by patient age, as reported by U.S. office-based physicians, January 1, 2009 - June 30, 2015

	01/2009-06/2015		
	Uses	Share	95% Confidence Interval
Total Market	6,353	100.0%	5945-6762
696 PSORIASIS/LIKE DISORDERS	6,353	100.0%	5945-6762
Age 0-17 years	13	0.2%	<0.5-32
methotrexate	7	56.9%	<0.5-22
adalimumab	3	23.3%	<0.5-12
acitretin	3	19.9%	<0.5-11
Age 18+ years	6,178	97.2%	5775-6581
etanercept	1,862	30.2%	1641-2084
methotrexate	1,836	29.7%	1616-2055
adalimumab	1,316	21.3%	1130-1502
ustekinumab	528	8.5%	410-646
apremilast	238	3.9%	159-317
acitretin	235	3.8%	156-313
infliximab	112	1.8%	57-166
cyclosporine	25	0.4%	<0.5-51
secukinumab	15	0.2%	<0.5-35
methoxsalen	7	0.1%	<0.5-21
hydroxyurea	4	0.1%	<0.5-15
Unknown Age	162	2.6%	97-228

Source: (b) (4) Jan 2009 - Jun 2015. Extracted September 2015. File: PDDA 2015-1236 Dx 696 molecule 9-23-15.xls

*Use – this term refers to the number of times a product linked to a diagnosis was captured for treatment of a particular disease.

3.2 LITERATURE REVIEW

A descriptive study by Wan et al. in 2011 assessed dermatologists' preference for first-line treatments of moderate to severe psoriasis in healthy adult patients. The study methods included a nationwide survey of a 1,000 randomly selected dermatologists who were members of the National Psoriasis Foundation or the American Academy of Dermatology. Of the 387 dermatologists (response rate 39%) that responded to the survey, the study found that the most preferred treatments for moderate to severe psoriasis in healthy adults were UVB phototherapy (male 39.5%; female 56.3%), etanercept (male 15.0%; female 18.6%), methotrexate (male 15.8%; female 4.4%), and adalimumab (male 11.6%; female 9.6%). Therapies with the least preferred response rate for first-line treatments of moderate to severe psoriasis in healthy adult patients were

ustekinumab (male 3.1%; female 1.3%), psoralen plus UVA (male 2.1%; female 2.6%), cyclosporine (male 0%; female 1.3%), alefacept (no longer available in the U.S. - male 0.3%; female 0.8%), and infliximab (male 0%; female 0.3%).¹

A review article by Sandoval et al. in 2014 found 46 publications that were used to provide an evidence-based update on systemic therapies for psoriasis. For this review, literature was searched from January 1, 2012 through July 1, 2013. A total of 18 systemic reviews on efficacy and safety and 28 randomized clinical trials (RCTs) were identified. Of the RCTs, 21 studies were reported for biologic therapy and 7 studies were reported for oral therapy. Sandoval et al. found favorable safety profiles for biologic agents (i.e. adalimumab, etanercept, infliximab and ustekinumab) when compared to traditional immunosuppressive/immunomodulatory systemic agents (methotrexate and cyclosporine). Sandoval et al. reported methotrexate as a first-line treatment for moderate to severe psoriasis and acitretin as a first-line treatment for chronic palmoplantar or pustular psoriasis. For biologic agents, first-line treatments include adalimumab, etanercept, and ustekinumab while infliximab is recommended as a second- or third-line biologic agent according to the consensus guidelines for the management of plaque psoriasis.²

Findings from a clinical review article by Herrier were similar to Sandoval et al. when comparing clinical trials of systemic agents for the treatments of moderate to severe psoriasis. Both Herrier and Sandoval et al. found that adalimumab, infliximab, and ustekinumab had favorable Psoriasis Area and Severity Index score (PASI-75 score)³ when compared to traditional oral systemic agents. Herrier defines traditional treatments for psoriasis as phototherapy, methotrexate, and cyclosporine. A summary of the clinical findings for each treatment is presented in the table below.³

Ref.	Agent	Dosage	% Pts Achieving Score	
			PASI-75	PASI-90
22, 28	Methotrexate	2–25 mg orally weekly	60	40
22, 28	Cyclosporine	3–5 mg/kg daily	50–71	33–50
27	Psoralen plus UVA light	8 mg oral psoralen	60	NA
21, 22	Acitretin	5 mg/kg orally daily	... ^b	...
39–44	Etanercept	50 mg subcutaneously biweekly for 12 wk and then 50 mg weekly	49–56.7	21
30, 37, 38	Adalimumab	80 mg subcutaneously initially and then 40 mg every 2 wk	71–88	45
33–36	Infliximab	3–5 mg/kg i.v. for wk 0, 2, and 6 and then every 8 wk	75–88	45
45–50	Alefacept	15 mg intramuscularly weekly for 12 wk	20	NA
44, 55, 56	Ustekinumab	45 mg subcutaneously for wk 0 and 4 and then every 12 wk ^c	67	42
		90 mg subcutaneously for wk 0 and 4 and then every 12 wk ^d	75–76	51–54

*PASI-75 = an improvement in the Psoriasis and Severity Index (PASI) score of at least 75% compared with baseline, PASI-90 = an improvement in PASI score of at least 90% compared with baseline, UVA = ultraviolet A, NA = not available.

^bBecause of acitretin's slow onset of action, PASI-75 scores at 10–16 weeks are not meaningful. Efficacy was variable but similar to that seen with psoralen plus UVA light.

^cDosage for patients weighing 100 kg or less.

^dDosage for patients weighing over 100 kg.

A review article by Kelly III et al. in 2015 examined clinical data on oral systemic therapies used in combination with ultraviolet phototherapy or biologic therapy for the

³ PASI-75 score = an improvement in the Psoriasis and Severity Index (PASI) score of at least 75% compared to baseline

treatment of psoriasis. The article included a comprehensive review of current non-biologic treatments for psoriasis based on a PASI-75 score. Kelly III et al. found that methotrexate was often used in combination with other oral systemic therapies, ultraviolet phototherapy, or biologic therapy. Cyclosporine was often used as a bridge therapy and prescribed concurrently with traditional or biologic therapies, then titrated down once response to therapy was obtained. Acitretin was also used in combination with ultraviolet phototherapy and biologic therapies. Acitretin was determined to be especially useful for pustular, palmoplantar or erythrodermic forms of psoriasis. Apremilast was suggested as a future therapy for the treatment of psoriasis. Mycophenolate mofetil, hydroxyurea, and 6-thioguanine (antimetabolite of azathioprine) should be used after patients have failed both oral systemic or biologic therapy. A summary of the clinical findings for each treatment is presented in the table below.⁴

Agent	Dose Range	Expected % PASI 75	Onset of Effect	Monitoring	Common Side Effects	Comments
Methotrexate	7.5–25 mg/wk as a single dose	40	Few weeks to months	CMP, CBC, pregnancy	Nausea, fatigue, HA, LFT abnormalities	Folate 1–5 mg/d Folic acid 15 mg/wk in 3 divided doses q 12 h, starting >6 h after methotrexate dose Avoid in alcohol abuse, hepatitis, pregnancy
Cyclosporine	3–5 mg/kg/d in 2 divided doses	60–70	Few weeks	CMP, CBC, magnesium, K, blood pressure	HA, HTN, increased creatinine, edema, nausea, hirsutism, gingival hyperplasia, tremor, infection, parathesia	Fast-acting, good rescue medication Prolonged use associated with toxicity Safe in pregnancy
Acitretin	10–50 mg/d, increased as needed; maximum 75 mg/d; single dose with fatty meal	20–40	Few months	CMP, lipids, CBC, pregnancy	Xerosis (general + mucous membrane), alopecia, peeling, erythema, lipid abnormalities, LFT abnormalities	More effective for palmoplantar, pustular, or erythrodermic variants; more effective in combination with psoralen-UV-A or ultraviolet B phototherapy; used safely in combination with other oral agents, topicals, and biologics. Avoid in women of childbearing age, alcohol abuse, dyslipidemia Extremely long half-life
Apremilast	30 mg bid	30	Few weeks to months	Weight*	HA, nausea, diarrhea, URI	Pregnancy C, registry for exposure reporting *No sustained lab abnormalities identified in phase II/III studies

Tofacitinib	5–10 mg bid	40–64	Several weeks	CBC, LFT, lipids	Infection, lymphopenia or neutropenia, LFT, lipid abnormalities herpes zoster	FDA approved for RA at 5 mg dose; safety concerns in RA at 10 mg Pregnancy C, registry for exposure reporting Avoid concomitant use with other immunosuppressive medications
Fumaric Acid Esters	Titrated up to maximum of 720 mg/d in 3 divided doses	40	Several weeks	CBC, LFT	Diarrhea, abdominal cramps, flushing, HA, eosinophilia, lymphopenia	Maximum dose requires tid administration Limited data Appears safe in pediatric population
Mycophenolate Mofetil	1–5 g/d in 2 divided doses	20	Few months	CMP, CBC, pregnancy	Nausea, diarrhea, CBC abnormalities, urinary symptoms	Significant number of partial responders and nonresponders Lack of long-term toxicity Pregnancy D
Hydroxyurea	500–1500 mg daily, as tolerated; alternately, 3–4.5 g/wk	40–50, yet poorly substantiated	Several months	CBC, pregnancy	gastrointestinal symptoms, rash, ulcers, alopecia	Poor quality data Pregnancy D
6-Thioguanine	120 mg twice per week, up to 160 mg thrice per week	50–80 yet poorly substantiated	Several months	CMP, CBC, pregnancy	Myelosuppression, liver toxicity	Poor quality data Pregnancy D
Sulfasalazine	1.5–4 g daily, as tolerated	<40	Several weeks	CBC, LFT, pregnancy	Anorexia, HA, nausea, vomiting, rash, oligospermia	Poor quality data Pregnancy B
Leflunomide	100 mg/d × 3 d loading dose, then 20 mg/d	17	Unclear	LFT, phosphate, CBC, pregnancy	Diarrhea, nausea, URI, HTN, HA, alopecia, rash	May benefit patients with significant PsA

Abbreviations: BP, blood pressure; CBC, complete blood count; CMP, comprehensive metabolic panel (electrolytes, renal, LFTs); HA, headache; HTN, hypertension; URI, upper respiratory tract infection.

Data from Nast A, Spornbeck B, Rosumeck S, et al. Which antipsoriatic drug has the fastest onset of action? Systematic review on the rapidity of the onset of action. *J Invest Dermatol* 2013;133(8):1963–70.

4 DISCUSSION

This review provides an analysis of data obtained from a proprietary drug utilization database available to the Agency and summaries of selected publications. Our analysis of U.S. office-based physician survey data found that etanercept, methotrexate, and adalimumab were the most common systemic drug therapies mentioned during physician office visits, associated with the treatment of psoriasis, from 2009 through June 2015. These three products accounted for 81% of all mentions for the treatment of psoriasis combined. Ustekinumab, acitretin, apremilast and infliximab accounted for 18% of all mentions combined. Conversely, cyclosporine, secukinumab, methoxsalen, and hydroxyurea were the least common systemic drug therapies and accounted for 1% of all mentions combined.

When comparing the U.S. office-based physician survey database results to the study by Wan et al. on dermatologists' preference for first-line treatments of moderate to severe psoriasis, we found that both sources were in agreement that etanercept, methotrexate, and adalimumab were the most preferred treatments. However, the Wan et al. article indicated that UVB phototherapy was the most preferred treatment overall. UVB phototherapy is not captured as a treatment option in our query of the U.S. office-based physician survey database since the database includes only drug therapies. Limitations of the Wan et al. descriptive study were the low response rates to the survey, which may limit the generalizability of the results to all U.S. dermatologists. Additionally treatment preference may vary by geographic region, access to phototherapy, and prior treatment experience.

Two review articles Sandoval et al. (2014) and Herrier (2011) reported favorable safety profiles for biologic agents (i.e. adalimumab, etanercept, infliximab and ustekinumab) when compared to traditional immunosuppressive/immunomodulatory systemic agents (methotrexate and cyclosporine). Sandoval et al. reported methotrexate, adalimumab,

etanercept, and ustekinumab as first-line treatment for moderate to severe psoriasis and acitretin as a first-line treatment for chronic palmoplantar or pustular psoriasis. For biologic agents, infliximab was recommended as a second- or third-line biologic agent.

We also found that traditional oral systemic therapies were often combined with other biologic or phototherapy for the treatment of moderate to severe psoriasis. Kelly III et al. found that methotrexate was often used in combination with other oral systemic therapies, ultraviolet phototherapy, or biologic therapy. Cyclosporine was used as a bridge therapy and prescribed concurrently with traditional or biologic therapies. Acitretin was used in combination with ultraviolet phototherapy and biologic therapies. Furthermore, acitretin was especially useful for pustular, palmoplantar or erythrodermic forms of psoriasis. Mycophenolate mofetil, hydroxyurea, and 6-thioguanine (antimetabolite of azathioprine should be used after patients have failed both oral systemic or biologic therapy.

5 CONCLUSION

In support of DDDP's clinical review of ixekizumab, we found that methotrexate, etanercept, and adalimumab were commonly associated with the treatment of psoriasis according to our analysis of U.S. office-based physician survey data. Less commonly used were cyclosporine, secukinumab, methoxsalen, and hydroxyurea, all of which were below the acceptable count to provide a reliable national estimate of use suggesting that these treatments may be used sparingly in the treatment of psoriasis.

Three publications that provided an evidence-based update on systemic therapies or phototherapy used to treat psoriasis found that biologic therapy is used first-line or in combination with oral systemic therapy or phototherapy. A descriptive study of dermatologists' preference for first-line treatments for moderate to severe psoriasis reported that UVB phototherapy was the most frequently preferred treatment followed by biologic therapy (i.e. etanercept, methotrexate, and adalimumab).

6 REFERENCES

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7 APPENDIX 1: DRUG USE DATABASE DESCRIPTION

(b) (4)

(b) (4)

is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The (b) (4) supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

PATTY A GREENE

10/01/2015

drug use data cleared by data vendor 09/28/15

MOHAMED A MOHAMOUD

10/02/2015

DAVID G MOENY

10/02/2015

Consultative Review and Evaluation of Clinical Data

DPP Consult #11536

Consultant Reviewer: Cara Alfaro, Pharm.D.
Clinical Analyst
CDER/ODE1/Division of Psychiatry Products (DPP)

Consultation Requester: Jane Liedtka, MD
Medical Officer
Division of Dermatologic and Dental Drug Products (DDDP)

Subject of Request: Ixekizumab (BLA 125521): treatment of moderate to severe psoriasis
Assessment of suicidality in clinical development program

Date of Request: 6/11/2015

Requested Completion Date: 8/7/2015

Background

The BLA for ixekizumab (IXE) for the treatment of moderate to severe psoriasis was submitted to the Division of Dermatologic and Dental Drug Products (DDDP) on 3/23/2015 (BLA 125521). IXE is a humanized IgG4 monoclonal antibody that binds with high specificity to IL-17A, a proinflammatory cytokine. A potential increased incidence of suicidal thoughts and behaviors have been noted in the clinical development program for brodalumab, another anti-IL-17A antibody, being developed for the treatment of psoriasis (IND (b) (4)). The Division of Psychiatry Products (DPP) has been involved in several consults and meetings with DDDP regarding the potential increased incidence of suicidal thoughts and behaviors with brodalumab. Secukinumab (Cosentyx) is another anti-IL-17A antibody approved on 1/21/2015 for the treatment of moderate to severe plaque psoriasis. Product labeling for secukinumab does not include any safety information regarding a risk of suicidal thoughts or behaviors.

DDDP consulted DPP to evaluate the potential suicidality signal in the IXE clinical development program. On 8/6/2015, DDDP notified DPP that the sponsor had submitted a retrospective C-CASA analysis of their data which had been requested by DDDP. DPP was unaware that DDDP had requested this analysis but this request was consistent with the advice DPP would have given the sponsor. DPP agreed to briefly review the C-CASA data and provide feedback to DDDP. DPP provided advice based on the initial consult as well as the C-CASA analyses at the internal Midcycle meeting on 8/11/2015. This consult serves as formal documentation of the advice already provided to DDDP.

IXE Clinical Development Program

In the ISS, the sponsor provided an evaluation of depression and “suicidality” in their clinical development program. The safety of ixekizumab in the treatment of moderate-to-severe plaque psoriasis was evaluated in the following studies:

- 3 pivotal Phase 3 studies

I1F-MC-RHAZ [Study RHAZ]; N = 1296; ixekizumab, placebo

I1F-MC-RHBA [Study RHBA]; N = 1224; ixekizumab, etanercept (active control), placebo

I1F-MC-RHBC [Study RHBC]; N = 1346; ixekizumab, etanercept (active control), placebo

- 4 supporting studies

I1F-MC-RHAG [Study RHAG] Phase 1, N = 46, ixekizumab, placebo

I1F-MC-RHAJ [Study RHAJ] Phase 2; N = 142; ixekizumab, placebo

I1F-JE-RHAT [Study RHAT] Phase 3 (open-label, Japanese patients); N = 90

I1F-MC-RHBL [Study RHBL] Phase 3 (randomized, open-label PK study); N = 204

The safety of ixekizumab was also evaluated in 4 studies in patients with rheumatoid arthritis (I1F-MC-RHAF [Study RHAF], I1F-MC-RHAK [Study RHAK], I1F-JE-RHAL [Study RHAL] and I1F-JE-RHAM [Study RHAM]).

Two of the Phase 3 pivotal trials (RHAZ, RHBA) included an induction dosing period (first 12 weeks) followed by a maintenance dosing period (Weeks 12-60) and an open-label long-term extension (weeks 60-264). The induction period was a comparison of the efficacy and safety of IXE to placebo (with or without the active comparator, etanercept). The maintenance dosing period was to evaluate the optimum dosing interval, maintenance of response/remission, relapse or rebound following treatment withdrawal and response to retreatment with IXE following relapse in a re-randomized population. In the maintenance phase, patients receiving IXE who were classified as responders were re-randomized to two different schedules of IXE (80 mg Q4W or Q12W) or placebo; nonresponders received IXE 80 mg Q4W. Study RHBC did not have a maintenance dosing period, after the induction period all patients received open-label IXE 80 mg Q4W in the long-term extension (weeks 12-264).

Dosing regimens examined during the induction dosing period included a Q2W regimen with a starting dose of 160 mg followed by 80 mg given as one SC injection every 2 weeks and a Q4W regimen with a starting dose of 160 mg followed by 80 mg given as one SC injection every 4 weeks. Dosing regimens examined during the maintenance dosing period included a Q4W regimen with 80 mg given as one SC injection every 4 weeks and a Q12W regimen with 80 mg given as one SC injection every 12 weeks.

The Phase 3 pivotal clinical trials excluded subjects with significant uncontrolled neuropsychiatric disorder, subjects with a history of a suicide attempt, subjects who score a 3 on

Item 12 (thoughts of death or suicide) on the Quick Inventory of Depressive Symptoms-Subject Rated 16-item scale (QIDS-SR16) scale at screening or baseline and subjects who are clinically judged by the investigator to be at risk for suicide.

To assess depression and suicidal thoughts and behaviors, the sponsor included a patient-rated scale, the QIDS-SR16. This scale includes a single item (Item 12 – thoughts of death or suicide) that assesses the presence of suicidal thoughts and behaviors. For the pivotal Phase 3 trials, the QIDS-SR16 was completed at screening, baseline and week 12 (end of the induction period), weeks 24, 36, 52 and 60 (end of maintenance period) and every 6 months thereafter in the long-term extension period.

QIDS-SR16

The QIDS-SR16 includes 16 items rated from 0 to 3. The scoring ranges from 0-27, however not each individual item is scored. For example, there are 4 items that rate sleep (e.g. falling asleep, sleep during the night, waking up too early and sleeping too much), for scoring, only the one sleep item with the highest severity score is included. Overall depressive symptom severity for QIDS-SR16 total scores is: 0-5 (none), 6-10 (mild), 11-15 (moderate), 16-20 (severe), 21-27 (very severe).

QIDS-SR 16 has one item for assessing suicidal thoughts/behaviors:

Item 12. Thoughts of death or suicide

- 0 I do not think of suicide or death
- 1 I feel that life is empty or wonder if it's worth living
- 2 I think of suicide or death several times a week for several minutes
- 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life

Reviewer comment: The QIDS-SR16 is an acceptable rating scale for assessing depressive symptoms in subjects.¹ However, the inclusion of only one item to assess suicidal thoughts and behaviors is not thought to be a comprehensive evaluation for these symptoms. While a rating of 0 would indicate a lack of suicidal thoughts or behaviors, ratings > 0 could indicate significant presence of suicidal thoughts. It is unclear whether there was any further follow-up with patients who rated > 0 on Item 12 to further determine the presence of suicidal thoughts and behaviors.

¹ Bernstein IH, Rush AJ, Stegman D, Macleod L, Witte B, Trivedi MH. A comparison of the QIDS-C16, QIDS-SR16, and the MADRS in an adult outpatient clinical sample. *CNS Spectrums* 2010;15:458-468.

Sponsor Analyses

The sponsor included analyses for suicidality by evaluating Item 12 of the QIDS-SR16 as well as suicide/self-injury adverse events in the ISS. The following databases were included in the ISS:

Primary Psoriasis Placebo-Controlled Integrated Analysis Set (Studies RHAZ, RHBA, RHBC)

Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)

Psoriasis Placebo- and Active-Controlled Integrated Analysis Set (Studies RHBA and RHBC)

All Psoriasis IXE Exposure Integrated Analysis Set

QIDS-SR16, Item 12 (thoughts of death or suicide)

For analysis of suicidal thoughts and behaviors, the sponsor evaluated Item 12 (thoughts of death or suicide) on the QIDS-SR16 categorically by comparing the percentage of patients categorized as improved (maximum postbaseline Item 12 score < baseline Item 12 score), worsened (maximum postbaseline Item 12 score > baseline Item 12 score) or stayed the same (maximum postbaseline Item 12 score = baseline Item 12 score). These analyses were conducted for the induction dosing period and maintenance dosing period.

Table 1. Sponsor Table.

**Table 2.7.4.92. QIDS-SR₁₆ Item 12 – Thoughts of Death or Suicide, Maximum Postbaseline Induction Period
Primary Psoriasis Placebo-Controlled Integrated Analysis Set
(Studies RHAZ, RHBA, and RHBC)**

Category	Placebo N=791 n (%)	80 mg Q4W N=1161 n (%)	80 mg Q2W N=1167 n (%)	Total IXE N=2328 n (%)	p-value
Nx	767	1129	1146	2275	
Improved	21 (2.7)	48 (4.3)	43 (3.8)	91 (4.0)	>0.999a
Worsened	17 (2.2)	19 (1.7)	17 (1.5)	36 (1.6)	
Same	729 (95.0)	1062 (94.1)	1086 (94.8)	2148 (94.4)	

Reviewer comment: For this categorical analysis for the Induction Dosing Period, the majority of patients continued to endorse the same score on Item 12 from baseline to postbaseline (stayed the same) and the percentages were similar between treatment groups. Similar numbers of patients were categorized as “worsened”, approximately 1.5-2% across treatment groups. One limitation of this type of analysis is that the magnitude of the categorical shift cannot be evaluated. For example, if all patients receiving placebo had a baseline score of 0 that worsened to a score of 1 but all patients receiving IXE had a baseline score of 0 that worsened to a score of 3, this would be a potentially significant difference not evaluated in this particular analysis.

Table 2. Sponsor Table

Table 2.7.4.96. QIDS-SR₁₆ Item 12—Thoughts of Death or Suicide, Maximum Postbaseline Score Compared to Baseline Score Induction Period Psoriasis Placebo- and Active-Controlled Integrated Analysis Set (Studies RHBA and RHBC)

Category	Placebo N=360 n (%)	ETN N=739 n (%)	80 mg Q4W N=729 n (%)	80 mg Q2W N=734 n (%)	Total IXE N=1463 n (%)	p-value ^a
Nx	346	722	711	721	1432	
Improved	12 (3.5)	18 (2.5)	34 (4.8)	32 (4.4)	66 (4.6)	>0.999
Worsened	9 (2.6)	20 (2.8)	12 (1.7)	11 (1.5)	23 (1.6)	
Same	325 (93.9)	684 (94.7)	665 (93.5)	678 (94.0)	1343 (93.8)	

Reviewer comments: This analysis is simply a subset of the data from Table 1 and includes the data for the active comparator, etanercept. This categorical analysis depicts similar percentages of patients who “worsened” in the placebo and etanercept groups with somewhat fewer patients who “worsened” in the IXE groups. Again, as above, there are limitations in the interpretation of these data as the magnitude of the shifts is not presented.

Table 3. QIDS-SR16 Item 12, Maximum Postbaseline Score Compared to Baseline Score Maintenance Dosing Period, Psoriasis Maintenance Integrated Analysis Set (Studies RHAZ and RHBA)

	Placebo (N = 402) n (%)	IXE 80 mg Q12W (N = 408) n (%)	IXE 80 mg Q4W (N = 416) n (%)	Total IXE (N = 824) n (%)
Nx	352	382	398	780
Improved	12 (3.4%)	13 (3.4%)	10 (2.5%)	23 (2.9%)
Worsened	9 (2.6%)	15 (3.9%)	6 (1.5%)	21 (2.7%)
Same	330 (94.0%)	355 (92.7%)	383 (96.0%)	738 (94.4%)

Source: Table 2.7.4.7.1.8.7 from Clinical Safety Summary

Reviewer comments: For this categorical analysis for the Maintenance Dosing Period, the majority of patients continued to endorse the same score on Item 12 from baseline to postbaseline (stayed the same) and the percentages were similar between treatment groups. Comparing categorical frequencies for patients who “worsened”, there were similar percentages comparing patients who received placebo and IXE (~2.6 – 2.7%) though slightly more were classified as “worsened” in the IXE 80 mg Q12W group (3.9%). Again, as above, there are limitations in the interpretation of these data as the magnitude of the shifts is not presented.

Suicide/Self Injury Adverse Events

To search for depression-related and suicidality events, depression was defined using the PTs from the Depression and Suicide/Self-Injury SMQ (MedDRA Version 17.0). According to the sponsor, the number and percentage of patients with treatment-emergent adverse events, SAEs

and AEs resulting in study drug discontinuation were summarized by treatment group using MedDRA PT nested within SMQ. Two summaries were created: pooling narrow and broad terms together and narrow terms only.

Altogether, the sponsor identified 9 suicide/self-injury events – all were suicide attempts:

Primary Psoriasis Placebo-Controlled Integrated Analysis Set (RHAZ, RHBA, RHBC):

Induction period – 2 reported suicide attempts (IXE 80 mg Q4W, IXE 80 mg Q2W)

Psoriasis Maintenance Integrated Analysis Set:

1 reported suicide attempt (IXE 80 mg Q12W)

All Psoriasis IXE Exposures Integrated Analysis Set:

The three cases as above and 2 additional events.

The sponsor indicated that “after database lock, 4 patients in the All Psoriasis Exposures Integrated Analysis Set reported suicide attempts which were captured in the LSS (Lilly Safety Systems database).” The sponsor provided vignettes for these patients. These 6 additional events (2 + 4) in the All Psoriasis Exposures Integrated Analysis Set were from studies RHAJ, RHAZ, RHBC, and RHBA.

The sponsor stated that in the Phase 1 study, RHAG, one placebo-treated patient reported a suicide attempt and suicidal ideation.

Reviewer comment: It is not clear that the sponsor has identified all potential cases of suicide/self injury using the methods described to identify the cases. By the description of the methodology, it appears that the sponsor only identified cases that resulted in study drug discontinuation (either discontinuation due to the event or other reasons) and this approach would not identify other cases that did not lead to study drug discontinuation. We would recommend that the sponsor perform a retrospective review of potential cases consistent with suicidal thoughts or behaviors using acceptable methodology.² This includes identification of potential cases including the text strings suic, overdos, attempt, cut, gas, hang, hung, jump, mutilate-, overdos-, self damage-, self harm, self inflict, self injur-, shoot, slash, and suic- and other related terms. The sponsor, Eli Lilly and Company, has extensive experience evaluating suicidal thoughts and behaviors in their psychiatric clinical development programs.

² Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA’s pediatric suicidal risk analysis of antidepressants. J Clin Psychiatry 2007;164:1035-1043.

Patient Narratives – Suicide Attempts

Patient narratives are provided in the Appendix to this consult. The narratives are primarily composed by the sponsor as vignettes and include some additional information from patient narrative standard output reports in the BLA submission.

Reviewer comment: For most of the cases (7/9), patients had a history of depression. Two of the cases had prior suicide attempts that were not disclosed to the investigator, subjects with a prior suicide attempt were excluded from these clinical trials. The two cases that occurred in the Induction phase of the protocols occurred at 52 and 71 days after starting IXE; the other cases occurred after receiving IXE for > 200 days (the latest event occurred 2 years after starting IXE). For most of these cases, the QIDS-SR16 Item 12 (thoughts of death or suicide) did not indicate suicidal thoughts or behaviors (score of 0), however the event may not have occurred close to completion of this scale in these protocols.

DDDP Questions

1. Is there a signal for suicidality with ixekizumab use?

It is difficult to definitively answer this question since it is not apparent that the sponsor has provided a comprehensive identification of potential suicide/self-injury adverse events cases. However, given this limitation, identification of nine cases of suicide attempt would suggest that IXE might be associated with suicidal thoughts and behaviors. Interpretation of these data is complex as there appears to be a significant background rate of depression and/or suicidal thoughts and behaviors in patients with psoriasis.

The sponsor cited data indicating that patients with psoriasis have a 39% increased risk of depression and the risk for depression increases with increasing severity with patients with severe psoriasis having a 72% increased risk of depression.³ The sponsor also cited published psoriasis clinical development programs having a prevalence of depression at baseline ranging from 14.6 to 40.3%. Regarding suicidality, the prevalence of suicidality reported in a population-based cohort study of 146,042 patients with mild psoriasis, 3956 patients with severe psoriasis and 766,950 patients without psoriasis (controls) was 0.71% in the mild psoriasis patients (vs. 0.39% in controls) and 1.01% in the severe psoriasis population (vs. 0.38% in controls).¹ It is beyond the scope of this consult to review all epidemiological data regarding the risk of depression and suicidal thoughts and behaviors in patients with psoriasis and it is noted that DDDP has consulted DEPI for this assessment. It does appear, however, that there is a significant background rate for both depression and suicidal thoughts and behaviors in this population which can complicate the interpretation of data for a new drug treatment/intervention.

³ Kurd SK, Troxel AB, Crits-Christoph P, Gelfand JM. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. Arch Dermatol 2010;146:891-895.

2. If not, could it have been obscured by exclusion of subjects with a prior history of suicidality?

It is not clear why subjects with any history of suicide attempts were excluded from these clinical trials. DDDP has stated that clinical development programs with other anti- IL-17A antibodies (e.g. brodalumab and secukinumab) have not had this exclusion criterion. In placebo-controlled clinical trials for major depressive disorder or bipolar I disorder, subjects with current suicidal ideation are excluded and subjects with a recent suicide attempt (e.g. within the past 3 months) are excluded. Exclusion of subjects with any history, however remote, of suicide attempt in the clinical development program for IXE may be overly conservative. It is not known whether inclusion of these subjects would impact the overall potential signal of suicidality associated with IXE.

3. Would you recommend labeling for risk of suicidality?

The finding of nine cases of suicide attempt in the clinical development program for IXE is of concern. It is also concerning that the identification of potential cases is incomplete and the rating scale used to prospectively assess suicidal thoughts and behaviors is not comprehensive. It is likely that further cases could be identified – e.g. suicidal ideation – that would be of additional concern from a safety perspective. However, it should also be acknowledged that there is a significant background rate of depression and suicidal thoughts and behaviors in patients with psoriasis.

DPP has been involved in the suicidal thoughts and behaviors safety signal for brodalumab. There has also been discussion as to whether this safety signal is a “class effect”. The brodalumab clinical development program included more rigorous prospective assessment of suicidal thoughts and behaviors (e.g. inclusion of eC-SSRS), such that it may be difficult to compare events between the brodalumab and IXE programs.

We note that DDDP has consulted with DEPI to review all epidemiological data regarding the risk of depression and suicidal thoughts and behaviors in patients with psoriasis. If this analysis confirms that the suicide attempt signal in the IXE program is in excess of the background rate, it would be appropriate to include these data in product labeling.

C-CASA Analyses

On 8/6/2015, the sponsor submitted a retrospective C-CASA analysis of the IXE clinical development program which was requested by DDDP. The sponsor did not identify any additional cases of suicidal thoughts or behaviors using this retrospective case analysis that were not identified in the prior submissions of suicide attempts (as above). The sponsor appeared to use the appropriate methodology to retrospectively identify these cases. Cases were reviewed by pairs of medical professionals internal to Eli Lilly who were described as trained in categorizing suicide-related events. These reviewers were blinded to study drug,

age, gender, race, ethnicity, weight, height and country and, upon further query, were also blinded to study design phase/period. The sponsor did not identify any cases of suicidal ideation using this methodology. The sponsor did identify 39 potential cases that were categorized as Not Enough Information. The sponsor provided narratives for these 39 cases, though this reviewer did not have adequate time to review these cases prior to the scheduled Midcycle sponsor meeting.

Reviewer comment:

It is somewhat unexpected that no cases of suicidal ideation were noted in the retrospective C-CASA analysis, given the number of cases of suicide attempt. This reviewer did not, however, review the 39 cases categorized as Not Enough Information. The sponsor does, however, have data that is consistent with suicidal thoughts in the QIDS-SR16 item 12 (thoughts of death or suicide) data. As discussed in the consult, the sponsor did evaluate worsening on the QIDS-SR16 item 12, but did not provide an analysis of the magnitude of the change on this item. It is also not clear whether there was any clinical follow-up for subjects rating > 0 on this item. To further evaluate the potential signal for suicidal thoughts/ideation, the sponsor should provide a shift analysis for the QIDS-SR item 12 data.

Please feel free to contact DPP if you have any further questions regarding this consult.

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Appendix

Patient Narratives – Suicide Attempts

Placebo controlled studies – Induction Phase

SAEs- depression, suicide attempt; DC due to SAE suicide attempt

A 29 YOWM (RHBA 456-6687) with a history of severe depression and 3 previous suicide attempts (per sponsor, undisclosed at time of enrollment) who was not taking any other concomitant medication, had a QIDS-SR16 total score of 3 (no depression) at screening and 8 (mild depression) at baseline. On Item 12 of the QIDS-SR16, the patient did not report having thoughts of suicide or death (score of 0) at the screening visit and at Visit 2 had a score of 1 (I feel that life is empty or wonder if it's worth living). Seventy-one days after receiving IXE 80 mg Q2W, the patient attempted suicide with an overdose of ibuprofen and codeine and was admitted to the hospital. During admission assessment by the hospital psychiatrist, the patient admitted he had been depressed for several weeks and that his suicide attempt was precipitated by losing his job and his girlfriend as well as having financial issues. On the same day of admission, the patient was discharged from the hospital to the care of his family; treatment with the antidepressant mirtazapine was initiated. Four days later, the patient was readmitted to the psychiatric facility for further treatment and was discharged 6 days later. At the end of the induction period, the patient's QIDS-SR16 total score was 2 (no depression) and Item 12 score was 0. The investigator learned of the hospitalization for depression and suicide attempt and, as required by the protocol, discontinued the patient from the study 16 weeks after initiation of study treatment with IXE. At the time of discontinuation, the patient's QIDS-SR16 total score was 7 (mild depression) and Item 12 was 0. Upon follow-up, the events of depression and suicide attempt were considered recovered.

SAE – suicide attempt, discontinuation due to AE depression

A 55 YOF (RHBA 216-4612) with a medical history of depression and alcohol abuse reported no concomitant medications and no history of previous suicide attempts. At screening and baseline, the QIDS-SR16 total score was 2 (no depression) and Item 12 score was 0. The patient was randomized to IXE 80 mg SC Q4W. Fifty-two days after starting study drug, the patient attempted suicide reportedly by injecting air intravenously. The patient had experienced a treatment emergent adverse event of depression of moderate severity at that time. It was stated that the reasons for the suicide attempt were because a friend had died and the patient had life-partner difficulties. No treatment was initiated. Approximately two weeks after the event, the QIDS-SR16 total score was 13 (moderate depression) and Item 12 was 2 (I think of suicide or death several times a week for several minutes). The patient was discontinued from study drug treatment. Approximately 3 months later, the patient recovered from the depressive episode.

Placebo controlled studies – Maintenance Phase

SAE - suicide attempt; discontinuation due to AE suicide attempt

A 39YOWM (RHBA 151-3006 reported a preexisting condition of mild depression starting 6 months prior to randomization and concomitant antidepressant medication (escitalopram), no prior suicide attempts were reported. Screening QIDS-SR16 total score was 0; baseline QIDS-SR16 total score was 3

(no depression) and baseline Item 12 score was 0. The patient was randomized to IXE 80 mg Q2W for the induction period. At the end of the 12-week induction period, the QIDS-SR16 total score was 12 (moderate depression) and Item 12 was 1 (I feel that life is empty or wonder if it's worth living). The patient was classified as an IXE responder and was re-randomized to IXE 80 mg Q12W for the maintenance period. After approximately 217 days on IXE and 134 days in the maintenance period, an SAE of suicide attempt was reported. The patient informed the investigator about a suicide attempt and indicated that he had been hospitalized for two suicide attempts within a 3-week timeframe; the patient did not provide information as to the mode of suicide attempt or treatment received. The last assessment of the QIDS-SR16 was at week 24 of the maintenance period, approximately 5 weeks prior to hospitalization for suicide attempt. At week 24, the QIDS-SR16 was 9 (mild depression) and Item 12 was 1 (I feel that life is empty or wonder if it's worth living). Because of the suicide attempt, the patient was scheduled for an early termination visit as required by the protocol; however, the patient declined to return to the investigative site or to provide consent for obtaining additional medical records.

All Psoriasis IXE Exposure dataset

SAEs - depression, suicide attempt (DC due to protocol violation)

A 69YOWM (RHAI 105-1507) reported no relevant medical history, no previous history of depression (although he had been previously treated with antidepressants), no other mental illness, no family history of depression and no history of substance abuse and no previous or reported history of suicide attempts. At baseline, the QIDS-SR16 total score was 2 (none) and Item 12 was 0. The patient was randomized to IXE 150 mg for the blinded treatment period and then received IXE 120 mg Q4W during the open-label period. The patient's last QIDS-SR16 assessment, per protocol, was at randomization for the open-label portion of the trial; QIDS-SR16 total score was 4 and Item 12 score was 0. Approximately 13 months after randomization and approximately 6 months after starting the open-label period, the patient reported experiencing severe depression and was started on the antidepressant bupropion by his primary care physician. At the Week 28 visit, the patient reported experiencing depression, study drug was administered, and bupropion was discontinued. One day after the Week 28 visit, the patient was admitted to a psychiatric hospital for depression treatment after a suicide attempt in which he attempted to slash his throat with a knife (described as a superficial laceration). The patient reported anhedonia, dysphoria, feelings of hopelessness, helplessness, impulsivity, stating the he had recently become increasingly distressed and overwhelmed due to multiple stressors (financial problems, recent retirement, poor coping skills, afraid of uncertain future). The patient was treated with the antidepressant citalopram and, 7 days after admission, was discharged with diagnosis of severe, recurrent major depression. The investigator noted that "the attempted suicide was most likely related to a recent death of a close friend...". The depression was considered recovered with sequelae, the attempted suicide was listed as recovered and the patient continued in the study. After 633 days on IXE and after 437 days in the open-label extension period, the patient was discontinued from the study due to a protocol violation – noted as the following on CRF "inclusion/exclusion criteria not met at beginning of study and subject discontinued when site and sponsor made aware of this", subject did not meet exclusion 19.

SAEs - depression, suicide attempt; DC due to SAE of depression

A 49 YOF (RHAZ 151-3001) had no history of depression and a prior history of anxiety (treated with venlafaxine). Further review of the case indicated that 8 years previously the patient had made a similar

suicide attempt (“cutting herself with a knife that was not sharp”). A history of suicide per protocol is an exclusion criterion. At screening, the QIDS-SR16 total score was 18 (severe) and Item 12 score was 0; at baseline the QIDS-SR16 total score was 12 (moderate) and the Item 12 score was 0. The patient was randomized to placebo during the induction period. At the end of the induction period (week 12), the QIDS-SR16 total score was 22 (very severe) and Item 12 was 0 (I do not think of suicide or death). For the maintenance period, she was classified as a nonresponder and assigned to IXE 80 mg Q4W in the long-term extension period. QIDS-SR16 total score at Week 24 was 20 (severe), at Week 36 was 20 (severe), at Week 52 was 20 (severe) and at Week 60 was 21 (very severe); Item 12 scores remained at 0 throughout the maintenance period. The last QIDS-SR16 total score prior to the AE was 8 (mild) at Week 84 with Item 12 score of 0. After 447 days on IXE, the patient was reported to have the adverse events of moderate depression and suicide attempt “non-life threatening attempted suicide”. The investigator reported that this suicide attempt was due to the patient’s husband have an affair and that a previous non-life threatening suicide attempt was intended to get her husband’s attention. The patient “cut herself and took a minor drug overdose”, no other details provided. The patient was hospitalized for a week and the non-life threatening attempted suicide was considered recovered that same day. The event of depression was ongoing, the patient was receiving the antidepressant mirtazapine and reportedly doing better. The patient discontinued the study due to depression.

SAEs - depression, suicide attempt

A 26 YO BM (RHBC 140-2855) had a medical history of bipolar disorder, depression and anxiety during the induction period while receiving IXE 80 mg Q2W. Screening QIDS-SR-16 total score was 13 (moderate) and Item 12 was 0. The baseline QIDS-SR16 total score was 12 (moderate) and Item 12 was 0. The patient was treated with divalproex sodium, quetiapine, perphenazine, gabapentin and carbamazepine and the anxiety and depression resolved and bipolar disorder continuing. At Week 12, QIDS-SR16 total score was 2 (none) and Item 12 was 0. At some point, patient discontinued meds, could not afford – not sure when. At Week 36, QIDS-SR16 total score was 0 (none) and Item 12 was 0; at Week 52, QIDS-SR 16 total score was 4 (none) and Item 12 was 0. Approximately 15 months after the start of the induction period and 12.5 months since starting treatment with blinded IXE in the extension period, the patient was hospitalized due to depression, suicidal ideation/suicide attempt, hallucinations and homicidal ideations/attempt (no details provided regarding homicidal ideations/attempt). He had also been taking MDMA (ecstasy) and marijuana. Prior to the hospitalization, the patient had been fired from his job for drug use and reported that he was feeling anxious, depressed and experiencing severe mood swings before being fired. The patient had also been recently arrested for a burglary but stated he had no recollection of the crime as he decided to end his life by overdose of MDMA. The patient was treated at the hospital with quetiapine, lorazepam and counseling. The patient was discontinued from the study.

SAEs - major depression, suicide attempt; DC due to subject decision

A 36 YOWF (RHBC 152-3058) had a history of major depressive disorder, no history of prior suicide attempts. She was on placebo during the induction period and started treatment with IXE in the open-label extension period. At Week 48, the patient stopped study drug so that she could receive a live vaccine. QIDS-SR16 total score at Week 0 was 9 (mild), Week 12 was 11 (moderate), Week 36 was 8 (mild), Week 48 was 3 (none); Item 12 scores were 0, 1, 1, and 0 respectively. Approximately 2 months

after the last dose of study drug, the patient was hospitalized for the reported events of major depressive disorder and left lower lobe pneumonia. Per patient, she was admitted to the hospital due to depression and an unsuccessful suicide attempt (alcohol and carbon monoxide). The SAE of suicide attempt was added to the patient summary after the initial reports of major depressive disorder and pneumonia. The patient reported worsening mood for three months in the context of numerous stressors including family issues and exacerbation of psoriasis. In the hospital, the patient was treated with citalopram and cognitive behavior therapy and is considered recovering from the major depressive episode. The patient completed the follow-up period and discontinued the study approximately one month after these events.

A 46 YOM (RHAZ 452-6568) with a history of bipolar disorder was randomized to placebo during the induction period and started treatment with IXE in the maintenance period and continued IXE in the open-label extension period. QIDS-SR16 total score at Week 0 was 4, Week 12 was 3, Week 24 was 3, Week 52 was 0, Week 60 was 3 and Week 84 was 3; corresponding Item 12 scores were 0 for all weeks. Two years after starting the study, and 25 days since his most recent dose of study drug, the patient attempted suicide by overdose of 24 diazepam tablets; he was referred for mental health assessment/hospitalization. The patient stated he took the tablets following domestic problems. The patient recovered the following day. The patient was discontinued from the study.

A 46 YOF (RHBA 486-6765) had a previous medical history of depression and concomitant medications included trazodone, bupropion, escitalopram and quetiapine. QIDS-SR16 total score at baseline was 15 (moderate), Week 12 was 12 (moderate), Week 24 was 12 (moderate), Week 36 was 21 (very severe), Week 52 was 11 (moderate) and Week 60 was 11 (moderate). Corresponding Item 12 scores were 0 for all weeks except for a score of 1 at Week 36. Approximately 11 months after starting the long-term extension period, the patient attempted suicide with pills and was hospitalized the following day. At the time of the initial report, the patient was still hospitalized and recovering from the event.

Placebo

SAEs – depression, suicide attempt

A 52 YOM (RHAG 007-1704) had a medical history of depression and suicide attempt. He began receiving study drug (placebo) every 2 weeks for 3 doses. Three months after last receiving study drug, the subject's depression worsened and he attempted suicide by hanging. Corrective treatment included citalopram, clonazepam, hydroxyzine, temazepam and quetiapine. The outcome of the event was recovered and he was discharged from the hospital approximately one week after the event.

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

/s/

CARA L ALFARO
08/25/2015

LUCAS P KEMPF
08/25/2015

I concur with this review and the concerns were transmitted to the Division and sponsor during the mid cycle meeting.

MITCHELL V Mathis
08/25/2015

Division of Epidemiology I

Date: June 22, 2015
Reviewer(s): Gabriella Anic, PhD, MPH, Epidemiologist
Team Leader: Sukhminder K Sandhu, PhD, MPH, MS, Team Leader
Division Director: David Shih, MD, MS, Deputy Director
Drug Name(s): Taltz (ixekizumab)
Subject: Post-marketing observational safety study
Application Type/Number: BLA 125521
Applicant/sponsor: Eli Lilly
OSE RCM #: 2015-793

On April 24, 2015, the Division of Dermatology and Dental Products (DDDP) requested that the Division of Epidemiology-1 (DEPI-1) review the sponsor's plan (b) (4)

(b) (4) The sponsor proposed (b) (4)

(b) (4) DEPI recommends that DDDP consider asking the sponsor to submit a short study concept proposal (Appendix A) with key study design elements to aid FDA in developing the PMR language. (b) (4)

Appendix A. Safety PMR Study Concept Outline for Evaluating Adverse Events in Patients Exposed to Taltz (ixekizumab)

Study Design	<ul style="list-style-type: none"> Describe the study design for the proposed safety PMR study. Describe how patients will be recruited into the study (e.g., routine clinical setting).
Study Objective(s)	<ul style="list-style-type: none"> State the primary and secondary objectives of the proposed study.
Entry Criteria	<ul style="list-style-type: none"> Describe inclusion and exclusion criteria for enrollment into the safety PMR study.
Data Source	<ul style="list-style-type: none"> Describe the data source and how data will be collected for medication use, adverse events, prior psoriasis treatments, and disease severity. Please indicate if there will be linkage to the Social Security Administration Master Death File or other death databases.
Study Population & Sample Size	<ul style="list-style-type: none"> Describe the comparator exposure arm(s). State the minimum number of patients to be enrolled in each arm and provide preliminary sample size and power calculations.
Follow-up	<ul style="list-style-type: none"> Provide the minimum length of follow-up and any patient censoring criteria. Describe plans to minimize missing data, especially for patients who are lost to follow-up.
Validation of Exposure/Outcome	<ul style="list-style-type: none"> Indicate how adverse events will be identified, (b) (4) Indicate how the study will validate and adjudicate exposures and outcomes.
Covariates	<ul style="list-style-type: none"> Indicate how the proposed study will collect information on the following potential confounding factors, including but not limited to: medical history, comorbidities, and concomitant medications.
Analysis Plan	<ul style="list-style-type: none"> Clearly state the hypothesis that will be tested in the primary analysis. Describe the statistical methods that will be used for the primary analysis and the methods to control for potential confounders. Describe any potential sensitivity analyses.

Milestones and Reporting	Propose dates for: <ul style="list-style-type: none">• Final Protocol Submission• Interim Report(s) Submission• Study Completion• Final Report Submission
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/s/

GABRIELLA M ANIC
06/22/2015

SUKHMINDER K SANDHU
06/22/2015

DAVID C SHIH
06/22/2015

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		
NDA # N/A BLA# 125521	NDA Supplement #: S- N/A BLA Supplement #: S- N/A	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: TALTZ Established/Proper Name: ixekizumab Dosage Form: solution for injection (pre-filled syringe and autoinjector) Strengths: 80 mg/mL		
Applicant: Eli Lilly Agent for Applicant (if applicable):		
Date of Application: 3/23/2015 Date of Receipt: 3/23/2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: 03/23/2016		Action Goal Date (if different):
Filing Date: 05/22/2015		Date of Filing Meeting: 4/28/2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): treatment of adult patients with moderate-to-severe plaque psoriasis 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) <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:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
The application will be a priority review if:	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<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)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <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 (FDCA Section 505B) <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)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 100834

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA 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 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</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

system.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	<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)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		1.1.3
<u>User Fee Status</u> <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 (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <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			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes, answer the bulleted	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

questions below:																							
<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? 				<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> 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"/>																		
<ul style="list-style-type: none"> 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)]? <p><i>If you answered yes to any of the above bulleted 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 for advice.</i></p>				<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>				Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<input type="checkbox"/>	<input type="checkbox"/>		
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																				
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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></p>																							
Exclusivity				YES	NO	NA	Comment																
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				<input type="checkbox"/>	<input checked="" type="checkbox"/>																		
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)]?				<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy																							
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?				<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																	
If yes, # years requested:																							
<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>																							

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" 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 the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.3.5.3

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 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<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 (3397/3792), 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"/>		1.1.2
<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"/>	1.1.2
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"/>		1.3.4
<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"/>		1.2
<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
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><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></p> <p><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></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.3.3
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><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></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 3/20/2014

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<i>pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , is there an agreed Initial Pediatric Study Plan (iPSP)? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.9.6
If required by the agreed iPSP , are the pediatric studies outlined in the agreed iPSP completed and included in the application? <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Partial Waiver (<6) and Deferral (>6 to <17)
<u>BPCA:</u> 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 checked="" 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 checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1.12.4
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 type="checkbox"/>	<input checked="" 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)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

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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? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Although not yet applicable, the applicant did submit in the PLLR format.
If PI not submitted in PLLR 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? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4/6/2015
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4/6/2015
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"/>	4/6/2015
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? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<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 type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
OSE/DMEPA/Human Factors: 4/6/2015				
CDRH devices: 4/7/2015				
CDRH Compliance: 4/7/2015				
SEALD PRO: 4/14/2015				
OSE/DEPI safety registry: 4/24/2015				
DPMH pregnancy registry: 4/24/2015				
OSI: clinical site inspection: 5/4/2015				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Date(s):				
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Pre-BLA mtg.
Date(s): <u>10/29/2014</u>				
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Date(s):				
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: 4/28/2015

BACKGROUND:

Ixekizumab is a humanized monoclonal antibody (IgG4) that binds and neutralizes IL-17A. Ixekizumab 80 mg/mL, either in a pre-filled syringe (PFS) or an autoinjector (AI), is intended for patient self-administration for the treatment of adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The FDA has issued 15 Advice/Information request letters for this program between May 2008 – September 2014. In addition, the FDA has provided feedback to the sponsor in 8 Guidance meetings and 1 Pre-BLA meeting. Of note, the sponsor did not have an EOP-2 meeting or SPA with the FDA.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Paul Phillips	Y
	CPMS/TL:	Barbara Gould	N
Cross-Discipline Team Leader (CDTL)	Jill Lindstrom		Y
Division Director/Deputy	Kendall Marcus		Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Jane Liedtka	Y
	TL:	Jill Lindstrom	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:	Matthew Guerra	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 protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Maria Cecilia Tami	Y
	TL:	Howard Anderson	Y
Biopharmaceutics	Reviewer:		
	TL:		
Quality Microbiology	Reviewer:	Bo Chi Colleen Thomas	N Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Jibril Abdus-Samad	Y
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Carlos Mena-Grillasca	Y
	TL:	Kendra Worthy	N
OSE/DRISK (REMS)	Reviewer:	Jasminder Kumar	N
	TL:	Jamie Wilkins-Parker	N
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	Reviewer:	Dhananjay Marathe	Y
	TL:	Jeffry Florian	N
Other attendees	Amy Egan Maria Walsh Wes Ishihara Nathan Caulk Ida Lina Diak Jessica Weintraub Robert Pratt Anita Brown Rakhi Dalal		

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:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
CLINICAL	<input type="checkbox"/> Not Applicable

<p>Comments: No review issues, but some informational requests for the 74-day letter.</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input 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 type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This biologic is not the first in class and does not present any novel issues that would warrant an AC discussion.
<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>CONTROLLED SUBSTANCE STAFF</p> <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
<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 <input type="checkbox"/> REFUSE TO FILE

<p>Comments: No review issues, but some informational requests for the 74-day letter.</p>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments: No items for 74-day letter</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>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: No items for 74-day letter</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 (protein/peptide products only)</p> <p>Comments: This aspect will be covered by the product quality and clinical pharmacology reviewers, not as a separate review discipline.</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>PRODUCT QUALITY (CMC)</p> <p>Comments: information provided does not allow for a biosimilarity comparison between EU and US sourced comparator (Etanercept).</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>New Molecular Entity (NDAs only)</p> <ul style="list-style-type: none"> Is the product an NME? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? 	<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

Comments:	
<u>Quality Microbiology</u> <ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? 	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments: The Eli Lilly S.A. – Irish Branch (FEI 3002806888) is ready for inspection	
<u>Facility/Microbiology Review (BLAs only)</u> Comments: DMF LOAs and nonclinical study report missing; IR sent to applicant by OPQ prior to filing.	<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
<u>CMC Labeling Review</u> Comments: Will request product samples (AI and PFS) with carton/container labeling on them.	<input type="checkbox"/> Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) <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? 	Information requested by OPQ and CDRH in pre-filing information request.
<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 type="checkbox"/> YES <input checked="" type="checkbox"/> NO (IR by OPQ and CDRH required for missing info)
<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	
<p>Signatory Authority: Julie Beitz</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 8/11/2015</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review

ACTIONS ITEMS	
<input checked="" 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, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone 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 type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

J P PHILLIPS
05/08/2015

BARBARA J GOULD
05/08/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Manufacturing and Quality
Respiratory, ENT, General Hospital, & Ophthalmic Devices Branch

Date: April 27, 2015
To: Jane Liedtka, MD
CDER/DDDP/WO22/Rm 5338, Tel: 301-796-0517, E-mail:
jane.liedtka@fda.hhs.gov
CC: Office of combination products at combination@fda.gov
Francisco Vicenty, Branch Chief, CDRH/OC/DMQ/REGO,WO-66, Rm 2642
From: Rakhi Dalal, Ph.D, Toxicologist, Consumer Safety Officer,
CDRH/OC/DMQ/REGO, WO-66, Room 2460
Applicant: Eli Lilly and Company
FEI: 1819470; Establishment DUNS Number: 006421325

Responsible Official: Brian E. Wagner, Pharm.D. Director, Global
Regulatory Affairs - US
Lilly Corporate Center
Indianapolis, IN 46285, US
Tel: (317) 276-4450, Fax: (317) 277-6917, E-mail:
wagner_brian_e@lilly.com

Contact Name: Rafiqah I. Williams, Vice President, Global Quality
Assurance Auditing
Lilly Corporate Center
Indianapolis, IN 46285, US
Tel: (317) 277-7036, Fax: (317)276-1838,
E-mail: williams_rafiqah_i@lilly.com

Form FDA 356h – Manufacturer & Responsibilities with Contact Name:
Rafiqah I. Williams, Vice President, Global Quality Assurance Auditing

1. Lilly Corporate Center
Indianapolis, IN 46285, US
FEI: 1819470; Establishment DUNS Number: 006421325
2. Eli Lilly S.A. – Irish Branch
Dunderrow, Kinsale
County Cork, Ireland, 99999
FEI: 3002806888; Establishment DUNS Number: 986500023

3.  (b) (4)

(b) (4)

4.

5.

6.

7.

8.

9.

Application # BLA 125521
Product Name: Ixekizumab, solution for injection, 80mg/1 mL
Proprietary Name: TALTZ™
Intended Use: This monoclonal antibody solution for injection comes in either a pre-filled syringe or an autoinjector. The product is intended to treat adult patients with psoriasis.
Consult Instructions: On 3/23/2015 CDER received a marketing application (BLA 125521) for ixekizumab 80 mg/mL with two delivery systems: prefilled syringe (PFS) and autoinjector (AI). DDDP requests a determination by CDRH/OC as to whether a device related inspection is required.

Background:

The consult request is from CDER/DDDP to provide an input on the BLA 125521, TALTZ™, Ixekizumab, solution for injection, 80mg/1 mL medical device constituents of the combination product. The Ixekizumab, solution for injection, 80mg/1 mL is composed of Ixekizumab 80mg/1 mL in glass (b) (4) syringe encased in the (b) (4) (b) (4) (b) (4) to create a finished PFS. The drug product remains exclusively in the glass primary container closure (b) (4) syringe, (b) (4) and does not contact the PFS, i.e., autoinjector. In addition to facility inspection review, documentation review of the combination product is performed. The deficiencies relevant to BLA 125521 are available on Page 11 of the memo, which can be communicated to applicant. CDRH, OC recommendations are on Page 12 for consideration.

Manufacturing Facility Review

Firm, FEI	Responsibility	Inspection history, FACTS, TURBO	Review Comment
<p>Lilly Corporate Center Indianapolis, IN 46285, US FEI: 1819470</p>	<p>Applicant. Drug substance manufacture and storage, Release and stability testing, Storage of the master and working cell banks, Drug product manufacture, Device assembly, packaging and labeling, Release and stability testing except potency</p>	<p>Inspected: 2/2-11/2015 NAI. Routine combination risk evaluation mitigation strategy (REMS) inspection and post-marketing adverse drug experience (PADE) inspection reported under FACTS assignment number (b) (4) and focused on both the Forteo and Axiron products. The firm's previous REMS inspection was on 2/11/13 and resulted in the issuance of a single item 483 for deficiencies regarding the accuracy of the firm's REMS system as it relates to the listing of certified pharmacies and health-care facilities. Correction to this observation was verified during the current inspection. The firm's previous PADE inspection was performed on 12/12/12 and resulted in the issuance of a 2 item 483 for the firm's failure to report all adverse drug experiences that are both serious and unexpected to FDA within 15 calendar days of receipt and to submit all follow-up information on adverse drug experience reports to FDA within required timelines. Corrections to these observations were verified during the current inspection. No inspectional observations were issued during the current inspection.</p>	<p>In the last inspection, the device constituent part of ixekizumab Prefilled syringe (PFS) manufacturing and assembly was not covered. CDRH recommends that in the next inspection, this facility be considered for device inspection with particular attention to Design control and non-conforming PFS. This facility has the capability of Adverse Event and Product Complaint Reports Procedures and CAPA which can be leveraged for QS reviews.</p>
<p>Eli Lilly S.A. – Irish</p>	<p>Drug product potency</p>	<p>Inspection: 12/19-</p>	<p>Review</p>

Branch, Dunderrow, Kinsale, County Cork, Ireland, 99999 FEI: 3002806888	release and stability testing	19/2015. VAI. Pre-approval inspection of the drug substance, ramucirumab manufacturing and related laboratory activities	recommendation defer to CDER
			(b) (4) Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER
			Review recommendation defer to CDER

Combination Product Description:

The ixekizumab PFS combination product consists of a device constituent part and a drug constituent part. The device constituent part consists of the components added to the drug

container to create the delivery device. The drug constituent part is the ixekizumab formulation in its primary container.

2.3.P.2.1 Components of the Drug Product

Ixekizumab solution for injection (also referred to as ixekizumab injection), is a clear to opalescent, colorless to slightly yellow (b) (4) sterile, (b) (4) parenteral solution for subcutaneous administration. Ixekizumab injection, 80 mg/1 mL, is supplied as a sterile solution in a 1 mL glass syringe, intended for single use. The commercial drug product formulation contains the active pharmaceutical ingredient, ixekizumab, in a matrix consisting of the inactive ingredients (b) (4) sodium chloride, polysorbate 80, and Water for Injection. The complete list of ingredients and quantitative composition on a per-unit basis for the ixekizumab drug product is provided in Table 2.3.P.1-1. Each syringe is filled to enable delivery of 1 mL.

Table 2.3.P.1-1 Composition of Ixekizumab Injection, 80 mg/1 mL

Ingredient	Quantity (mg/mL)	Function	Reference to Standards
Active Ingredient			
Ixekizumab	80	Active Ingredient	Internal Standard: See Section 2.3.S.4.1, Specifications
Other Ingredients			
Sodium Citrate Dihydrate	5.11	(b) (4)	USP, Ph.Eur., JP
Citric Acid Anhydrous	0.51		USP, Ph.Eur., JP
Sodium Chloride	11.69		USP, Ph.Eur., JP
Polysorbate 80	0.30		USP, Ph.Eur., JP
Water for Injection	(b) (4)		USP, Ph.Eur., JP

2.3.P.2.2.1 Formulation Development

Three ixekizumab formulations were utilized throughout the clinical development program (b) (4) the following compositions:

(b) (4)

- Solution Formulation (Phase 3 and limited Phase 2): 80 mg ixekizumab in 5.1 mg sodium citrate dihydrate, 0.51 mg citric acid anhydrous, (b) (4) mg sodium chloride, and 0.30 mg polysorbate 80 per mL.

The Phase 1 clinical trials were conducted using (b) (4) while Phase 2 clinical studies were conducted using (b) (4). The Phase 3 and Phase 2 (limited use) studies were conducted using a solution formulation, 80 mg. The ixekizumab for injection, (b) (4) drug product were developed based on preformulation and early phase clinical development formulation design studies. The (b) (4) drug products were supplied in a Type I glass container with an (b) (4) closure. Firm indicates stability of the DP at 2-8 C for at least 24 months. (b) (4)

(b) (4)

The ixekizumab solution formulation was developed and optimized based on preformulation studies, pharmaceutical development experience and statistical Design of Experiments (DOE) studies. The ixekizumab injection was supplied as an 80 mg/mL solution drug product in a 1 mL glass (b) (4) syringe (b) (4) assembled into a delivery device for subcutaneous administration.

To support the transition from the (b) (4) drug product vial to the (b) (4) syringe container closure system, the component characteristics pertinent to the (b) (4) syringe system, (b) (4) needle shield and plunger were characterized and evaluated to ensure compatibility with ixekizumab, in Section 3.2.P.2.4, Container Closure System.

3.2.P.7.1 Primary container closure system Description

The primary container closure system for ixekizumab injection is a 1 mL-long clear glass syringe barrel with small round flange, 27G (b) (4) x 1/2" staked needle, and closed with a (b) (4) plunger and rigid needle shield, Figure 3.2.P.7.1-1.

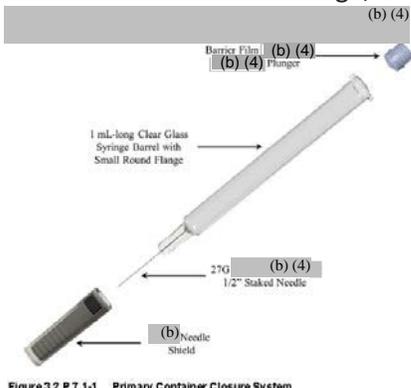


Table 3.2.P.7.2-1 Container Closure System Identification for Ixekizumab Injection, 80 mg/1 mL

Component	Description
Syringe Barrel	(b) (4) Type I clear glass 1 mL-long syringe barrel with small round flange, 27G (b) (4) 1/2" staked needle, and (b) (4) needle shield
Plunger	(b) (4) (b) (4) plunger

Figure 3.2.P.7.1-1 Primary Container Closure System

3.2.P.7.3 Container Closure System Component Supplier Information

The syringe barrel and plunger are received ready-to-use from the suppliers. Component supplier information is provided in Table 3.2.P.7.3-1. Letters of Authorization for the DMFs described in Table 3.2.P.7.3-1 are provided in Module 1, Section 1.4.2. These letters give FDA permission to reference supplier drug master files on behalf of Eli Lilly and Company.

Table 3.2.P.7.3-1 Container Closure System Component Supplier Information

Component/Process	Supplier	Drug / Device Master File Number
Syringe Barrel	(b) (4)	(b) (4)
Needle Shield (b) (4)	(b) (4)	(b) (4)
Plunger (b) (4)	(b) (4)	(b) (4)

3.2.P.3.3 Description of Manufacturing Process and Process Controls

(b) (4)



Table 3.2.P.5.1-1 Specifications for Ixekizumab (b) (4) Syringes

Test	Analytical Procedure	Acceptance Criteria	
		Release	End of Shelf-life
Identification Test			
Identity	(b) (4)	Conforms to the ixekizumab reference standard.	--
Identity	Cell-Based Bioassay	Conforms to the ixekizumab reference standard.	--
Quantity Test			
Quantity	UV	Not less than (b) (4) and not more than (b) (4) the label claim (equivalent to not less than (b) (4) and not more than (b) (4))	Not less than (b) (4) the label claim (equivalent to not less than (b) (4) and not more than (b) (4))
Potency Test			
Potency	Cell-Based Bioassay	Not less than 75% and not more than 130% potency relative to the potency of ixekizumab reference standard	Not less than 75% and not more than 130% potency relative to the potency of ixekizumab reference standard
Purity Tests			
Purity	SEC	Not less than (b) (4)	Not less than (b) (4)
Total Aggregates	(b) (4)	Not less than (b) (4)	Not less than (b) (4)
Purity	CE-SDS	Not less than (b) (4)	Not less than (b) (4)
Purity	CE-SDS	Not less than (b) (4)	Not less than (b) (4)

Table 3.2.P.5.1-1 (continued) Specifications for Ixekizumab (b) (4) Syringes

Test	Analytical Procedure	Acceptance Criteria	
		Release	End of Shelf-life
Other Tests			
Description	Visual	Clear to opalescent, colorless to slightly yellow (b) (4) (b) (4)	Clear to opalescent, colorless to slightly yellow (b) (4)
Charge Heterogeneity			
Main Peak	(b) (4)	Not less than (b) (4) and not more than (b) (4)	Not less than (b) (4) and not more than (b) (4)
Total Acidic Variants	(b) (4)	Not less than (b) (4) and not more than (b) (4)	Not less than (b) (4) and not more than (b) (4)
Total Basic Variants	(b) (4)	Not less than (b) (4) and not more than (b) (4)	Not less than (b) (4) and not more than (b) (4)
Polysorbate 80:	HPLC-UV	--*	Not less than (b) (4)
Bacterial Endotoxins	USP <85>	Not more than (b) (4) EU/mg	--
Particulate Matter			
Particles	(b) (4)	Not more than (b) (4) part/container	Not more than (b) (4) part/container
Particles	(b) (4)	Not more than (b) (4) part/container	Not more than (b) (4) part/container
Sterility	USP <71>	Meets USP <71> requirements	Meets USP <71> requirements
pH	USP <791>	Not less than (b) (4) and not more than (b) (4)	Not less than (b) (4) and not more than (b) (4)

Table 3.2.P.5.1-2 Specifications for Ixekizumab Pre-Filled Syringe

Test	Analytical Procedure	Acceptance Criteria
Identity	(b) (4)	Conforms to the ixekizumab reference standard
Dose Accuracy	Volume by weight	A 95% confidence/95% probability content tolerance interval is (b) (4)
Visual/Functional Inspection	Manual Inspection	Pass

Ixekizumab Prefilled Syringe: The ixekizumab Prefilled Syringe (PFS) was developed and designed according to Design Controls described in 21 CFR 820.30, Quality System Regulation, at Eli Lilly and Company, Pharmaceutical Delivery Systems (PDS), Indianapolis, Indiana. References to the procedures and standards followed during the design, development and manufacturing of the PFS are provided in Section 2.3.P.7 Medical Device - Auto-injector.

The sterilized syringe system is a 1-mL glass syringe with a staked needle, used as the container closure system for ixekizumab (b) (4) and is indicated to comply with the requirements of ISO 11040-4 and ISO 7864. The proposed commercial version of the prefilled syringe is shown in Section 3.2.P.7, Medical Device – Prefilled Syringe.

The external components of the PFS consisting of the plunger rod, finger grips, flange cap, syringe body (casing around the syringe barrel), needle cap and cap insert components are designed for use with Lilly parenteral drug products that are filled in a 1-mL, long glass syringe with a staked needle. The (b) (4) is enclosed within the PFS parts and the parts of the PFS do not contact the drug product. The combined (b) (4) and the PFS parts form a prefilled, single-use injection device that delivers the fixed dose of drug product to the subcutaneous tissue. The length of the needle on the (b) (4) is commonly used for approved syringes for subcutaneous delivery.

The materials used to surround the (b) (4) syringe (b) (4) (b) (4) have been selected for their particular physical properties. These exterior materials do not contact the drug product. In the future, materials that meet these selection criteria and

do not adversely impact ISO requirements may be used. Also should any material changes be made in the future, the applicable requirements of design control including appropriate validation will be followed prior to implementation. Material properties and data sheets, manufacturing processes, shelf-life storage conditions and in-use conditions, component design, and system design were assessed to ensure the shelf life of the PFS exceeds the dating of ixekizumab.



To use the PFS, the needle cap is removed and discarded and the user inserts the needle in the skin. The needle insertion depth is controlled by the user. The plunger rod is depressed until all the fluid is injected. The movement of the plunger expels the fixed dose volume that is defined by the fill volume of the drug container. The user then removes the needle from the skin and disposes the PFS in a sharps container.

Activation of autoinjector, verbatim: The activation end of the auto-injector incorporates a lock feature, the Lock Ring, to prevent unintentional activation and an Injection Button to start the injection sequence. The injection end incorporates a Base Cap for needle shield removal and a Clear Base for stable positioning at the injection site.

The user activates the device by pressing the Injection Button to initiate the injection cycle. Pressing the Injection Button generates an audible and tactile click and the device automatically

inserts the needle, injects the drug product and following a delay to ensure that the entire contents of the syringe are delivered, retracts the needle.

The user must hold the device against the skin during the injection cycle but is not required to maintain pressure on the Injection Button. The device generates an audible and tactile click at the end of the needle retraction process. The device locks the retracted needle in place for disposal of the used auto-injector in a sharps container.

Table 3.2.P.5.1-3 Specifications for Ixekizumab Auto-Injector

Test	Analytical Procedure	Acceptance Criteria
Identity	(b) (4)	Conforms to the ixekizumab reference standard
Dose Accuracy	Volume by weight	A 95% confidence/95% probability content tolerance interval is (b) (4)
Visual/Functional Inspection	Manual Inspection	Pass
Injection Process Time	Activation to retraction timing	A 95% confidence/95% probability content upper tolerance limit (b) (4) (b) (4)

Drug and Device Compatibility

The exterior components of the ixekizumab PFS do not contact the drug product. The drug product remains in the primary container closure (b) (4) when assembled in the PFS. The fluid path of the drug product into the body is through the staked sterile needle in the single-use system.

The device constituent part of the combination product is classified as a surface-contacting device in contact with intact skin.

Assembly Process

The PFS is manufactured (b) (4)
(b) (4)

(b) (4) (b) (4) A description of the assembly process is provided in Section 3.2.P.7, Medical Device – Prefilled Syringe.

Assembly Process Validation

Process Failure Mode and Effect Analyses (pFMEA) was performed for the assembly line to define a risk based approach to process qualification and validation. The PFS assembly process validation strategy included the following:

- 1) A total of three (3) process validation batches.
- 2) Statistically-based sampling plans to provide understanding of the defect level across several assembly conditions.
- 3) Additional design verification testing to verify that the assembly process did not impact the functional performance of the PFS.
- 4) Analytical drug product testing on finished PFS to verify the assembly process did not impact the drug product quality.

Process validation data also considered meeting acceptance criteria; intactness of DP quality due to the assembly process, including container closure integrity, verification that the control

strategy is adequate to control routine batch release with consistent and reproducible yield for quality requirements.

Quality System Management of the Control Strategy

The control strategy is maintained throughout the product lifecycle via the internal quality system including deviation management, change management and periodic reviews. These quality system elements ensure that the manufacturing control strategy (including critical and non-critical controls) is maintained throughout the product lifecycle to ensure product quality and compliance with regulatory documentation.

2.3.P.3.5.2 Sterilization Process and Validation Summary

The sterility of ixekizumab (b) (4) syringes is assured through a series of controls,

(b) (4)

(b) (4) A comprehensive quality assurance risk management program has been established in which risk assessments are conducted to document the prevention and detection controls.

Review Comment: The exterior components of the ixekizumab prefilled Syringe (PFS) is manufactured (b) (4) (b) (4) to create a finished PFS.

The drug product remains exclusively in the glass primary container closure (b) (4) (b) (4) and does not contact the PFS, i.e., autoinjector. The device (b) (4) (b) (4) is a Class II medical device, however not cleared by CDRH. During use, the fluid path of the drug product to the patient is through the staked sterile needle in the single-use system. It appears that the medical device aspects of the ixekizumab auto-injector were developed and designed according to Design Controls described in 21 CFR 820.30, Quality System Regulation, at Eli Lilly and Company, Pharmaceutical Delivery Systems (PDS), Indianapolis, Indiana. However no information on the design inputs, outputs, verification and design transfer (21 CFR 820.30) is provided. The firm indicates that possible changes may be made to the PFS materials. Change controls although mentioned however does not provide the depth of activities which may be impacted during manufacturing processes of the combination product. The performance for the design input is deferred to CDRH/ODE.

Deficiencies to be conveyed to the applicant

The following deficiencies were identified while conducting a documentation review of BLA125521, in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product, and it is requested that the below be communicated to the firm:

1. You indicate that the exterior components of the ixekizumab prefilled Syringe (PFS) is manufactured (b) (4) (b) (4) to create a finished PFS. The drug product remains exclusively in the glass primary container closure (b) (4) (b) (4) and does not contact the PFS, i.e., autoinjector. You state the device (b) (4) (b) (4) is a Class II medical device and indicate that the medical device aspects of the ixekizumab auto-injector were developed and designed according to Design Controls described in 21 CFR 820.30, Quality System Regulation, at Eli Lilly and Company, Pharmaceutical Delivery Systems (PDS), Indianapolis, Indiana. In the submission limited information related to ixekizumab prefilled Syringe (PFS) associated with

21 CFR 820.30 is provided. Please provide detailed summary for the Design Control per 21 CFR 820.30 as it relates to ixekizumab prefilled Syringe (PFS).

2. In BLA 125521 you state: In the future, materials that meet these selection criteria and do not adversely impact ISO requirements may be used. Please be informed that although changes to the medical device constituents can be made during the phase 3 with appropriate qualifications, relevant information and specifications to confirm that the combination product did not change in regards to final specifications should be provided to FDA for review. Please be advised that any changes to the combination product done during the phase are subject to design controls (21 CFR 820.30).

In addition, please provide the following summaries for FDA desk reviews.

- a. Complete information regarding compliance with 21 CFR 820.20, Management Controls
- b. Purchasing Controls as per 21 CFR 820.50
- c. Corrective and Preventive Action as per 21 CFR 820.100. There was no information available for review regarding the establishment of a CAPA system compliant with 21 CFR 820.100.
- d. Facilities responsible for developing the design specifications of the device constituent part and maintenance of the design history file.

Please refer to suggestions on the types of documents to submit for review related to the applicable 21 CFR Part 820 regulations, available in the guidance document "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," February 3, 2003. The complete document may be found at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>

This application was deficient overall. Additional information is required for an adequate desk review.

CDRH Office of Compliance Recommendation

The Office of Compliance (OC) at CDRH has completed the evaluation of application BLA 125521 and has the following recommendations:

1. CDRH, OC recommends BLA 125521 filable.
2. CDRH, OC recommends that in the next inspection, this facility be considered for device inspection.
3. Prior to the applicant responding to the deficiencies identified above, CDRH, OC is open to having an interactive discussion.
4. Application BLA 125521 approvability under the Medical Device Regulations should be delayed until the sponsor provided the additional information requested and an adequate desk review of the application has been completed.

Rakhi M.

Panguluri -S

Digitally signed by Rakhi M.
Panguluri -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
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Date: 2015.04.28 11:45:21 -04'00'

Rakhi Dalal, Ph.D.

Prepared: RDalal: 4/27/2015
Reviewed: FVicenty: 4/28/2015

CTS No.: ICC1500182
BLA 125521

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

/s/

J P PHILLIPS

04/30/2015

This CDRH consult filing review is being entered into DARRTS on behalf of the reviewer, Rakhi Dalal, who does not have access to DARRTS.

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: BLA 125521

Application Type: New BLA

Name of Drug/Dosage Form: ixekizumab injection, 80 mg/mL

Receipt Date: March 23, 2015

Goal Date: March 23, 2016

1. Regulatory History and Applicant's Main Proposals

On 10/29/2014 the FDA held a pre-BLA meeting with the applicant. On March 23, 2015 the applicant submitted a new BLA under section 351(a) of the PHS Act. Their submission included proposed labeling in the PLR format.

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 the process of labeling discussions.

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

- 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 unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.

Selected Requirements of Prescribing Information

Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been 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:

- YES** 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 the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- 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

Selected Requirements of Prescribing Information

- 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**.

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:

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:

Selected Requirements of Prescribing Information

- 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** 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

- NO** 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: *The manufacturer phone number uses alphabetical characters with the numerical equivalent in parenthesis. The numbers should come first and the alphabetical characters can be in parenthesis.*

Patient Counseling Information Statement in Highlights

- NO** 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:

Selected Requirements of Prescribing Information

- “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:** To follow the above convention for Medication Guide, the words "FDA-approved" need to be removed from the Highlights statement.*

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

- NO** 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: *The applicant has chosen to follow the new PLLR guidance. Therefore the new section 8.2 is correctly titled "Lactation" rather than "Labor and Delivery". Because this is consistent with the new PLLR, this is not a comment for the applicant.*

- 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]

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

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/

J P PHILLIPS
04/27/2015