APPLICATION NUMBER:

761055Orig1s000

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.

<table>
<thead>
<tr>
<th>BLA #</th>
<th>BLA 761055</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Dupixent (dupilumab) Injection, 150 mg/mL</td>
</tr>
</tbody>
</table>

**PMR Description:** Conduct a randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of dupilumab administered concomitantly with topical therapy in subjects, 6 years to less than 12 years of age, with severe atopic dermatitis.

**PMR Schedule Milestones:**
- Final Protocol Submission: 03/2018
- Trial Completion: 06/2019
- Final Report Submission: 09/2019

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
   - [x] Other

   The adult trials are completed and ready for approval.

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 Phase 3 trials were conducted in adults 18 years and older. Atopic dermatitis most commonly occurs in pediatric age groups. This trial is need to establish the efficacy and safety of dupilumab when administered concomitantly with topical therapy in subjects 6 to < 12 years of age.
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.

   An effectiveness and safety clinical trial in subjects 6 to <12 years.

   **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.

<table>
<thead>
<tr>
<th>BLA #</th>
<th>BLA 761055</th>
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<tbody>
<tr>
<td>Product Name:</td>
<td>Dupixent (dupilumab) Injection, 150 mg/mL</td>
</tr>
<tr>
<td>PMR Description:</td>
<td>Conduct a randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of dupilumab monotherapy in subjects, 12 years to less than 18 years of age, with moderate-to-severe atopic dermatitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PMR Schedule Milestones:</th>
<th>Final Protocol Submission: 01/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Completion:</td>
<td>02/2019</td>
</tr>
<tr>
<td>Final Report Submission:</td>
<td>05/2019</td>
</tr>
</tbody>
</table>

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
   - [x] Other

   Adult trials are completed and ready for approval.

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 Phase 3 trials were conducted in adults 18 years of age and older. Atopic dermatitis most commonly occurs in pediatric patients. This trial is needed to establish the efficacy and safety of dupilumab when administered concomitantly with topical therapy in pediatric subjects 12 years to < 18 years of age.
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
  - [x] 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.

   An effectiveness and safety clinical trial in subjects 12 to <18 years.

**Required**

- [ ] Observational pharmacoepidemiologic study
- [ ] Registry studies
- [x] 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

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<th>BLA #</th>
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<tbody>
<tr>
<td>Product Name:</td>
<td>Dupixent (dupilumab) Injection, 150 mg/mL</td>
</tr>
</tbody>
</table>

PMR Description: Conduct an open-label trial to characterize the long-term safety of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe atopic dermatitis

PMR Schedule Milestones:
- Final Protocol Submission: 04/2018
- Trial Completion: 12/2022
- Final Report Submission: 03/2023

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
- [x] Long-term data needed
- [ ] Only feasible to conduct post-approval
- [ ] Prior clinical experience indicates safety
- [ ] Small subpopulation affected
- [ ] Theoretical concern
- [ ] Other

The adult trials are completed and ready for approval.

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.”

Open-label study to characterize the long-term safety of dupilumab in pediatric subjects 6 months to < 18 years with moderate and/or severe AD. This study will enroll subjects who participated in the pharmacokinetic or efficacy pediatric studies/trials, who remain qualified to continue open-label treatment according to the inclusion/exclusion criteria of the extension study.
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.

   | An open-label study to characterize the long-term safety of dupilumab in pediatric subjects 6 months to < 18 years with moderate and/or severe atopic dermatitis. Duration of exposure to dupilumab should be 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

☐ 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.

BLA #
BLA 761055

Product Name:
Dupixent (dupilumab) Injection, 150 mg/mL

PMR Description:
Conduct a safety, pharmacokinetic (PK), and efficacy trial in subjects 6 months to less than 6 years with severe atopic dermatitis.

PMR Schedule Milestones:
Final Protocol Submission: 01/2018
Trial Completion: 08/2021
Final Report Submission: 11/2021

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

The adult trials are completed and ready for approval.

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 Phase 3 trials were conducted in adults 18 years of age and older. Correct dosing needs to be established for patients 6 months to < 6 years. Incorrect dosing could result in unnecessary exposure in these patients, which could be associated with increased adverse events. The trial is to characterize the safety, PK, and efficacy of dupilumab in pediatric patients, 6 months to < 6 years of age with severe atopic dermatitis.
3. If the study/clinical trial is a **PMR**, check the applicable regulation.  
*If not a PMR, skip to 4.*

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

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**
  - Assess a known serious risk related to the use of the drug?
  - Assess signals of serious risk related to the use of the drug?
  - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**
  - Analysis of spontaneous postmarketing adverse events?  
    *Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

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

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

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

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

   The trial is to characterize the safety and PK of dupilumab in pediatric patients 6 months to less than 6 years of age with severe AD. The trial should be conducted in 2 parts: Part A: open-label study to evaluate the safety and PK; Part B: randomized, double-blind, parallel group placebo-controlled trial to evaluate efficacy and 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)

Reference ID: 4075523
PMR/PMC Development Template

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

BLA # BLA 761055
Product Name: Dupixent (dupilumab) Injection, 150 mg/mL

PMR Description: Conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab 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 Schedule Milestones:

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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</thead>
<tbody>
<tr>
<td>Final Protocol Submission</td>
<td>12/2018</td>
</tr>
<tr>
<td>Study Completion</td>
<td>07/2025</td>
</tr>
<tr>
<td>Final Report Submission</td>
<td>07/2026</td>
</tr>
</tbody>
</table>

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.

- [X] 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.”
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
- Immuneogenicity 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 or clinical trial performed for effectiveness

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

<table>
<thead>
<tr>
<th>BLA #</th>
<th>BLA 761055</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name</td>
<td>Dupixent (dupilumab) Injection, 150 mg/mL</td>
</tr>
</tbody>
</table>

**PMR Description:** Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to dupilumab and a non-dupilumab systemic medication or phototherapy 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 atopic dermatitis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

<table>
<thead>
<tr>
<th>PMR Schedule Milestones</th>
<th>Final Protocol Submission:</th>
<th>03/2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study Completion:</td>
<td>10/2025</td>
</tr>
<tr>
<td></td>
<td>Final Report Submission:</td>
<td>10/2026</td>
</tr>
</tbody>
</table>

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.

   - [x] 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.”
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.

BLA #: BLA 761,055
Product Name: Dupixent (dupilumab) Injection, 150 mg/mL

PMC Description: Complete the ongoing drug-drug interaction clinical study R668-AD-1433 to determine the potential for dupilumab to alter the pharmacokinetics of CYP substrates in subjects with moderate-to-severe atopic dermatitis (AD).

PMC Schedule Milestones: Final Report Submission: 06/2017

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

   The Applicant is currently conducting a clinical drug-drug interaction study (R668-AD-1433) to evaluate the potential effects of dupilumab on the PK of CYP450 substrates in adult patients with moderate-to-severe atopic dermatitis (AD). The results of study R668-AD-1433 were not available at the time of BLA submission. The study is not required for approval. The PMC will request that the Applicant complete this ongoing drug interaction study.

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.”
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.

---

There is a potential for AD disease-drug-drug interaction based on the current understanding that AD patients have elevated proinflammatory cytokines. The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-4, IL-6, IL-10, IL-13, TNFα, and IFN) during chronic inflammation. Thus, dupiluamb, an antagonist of IL-4Rα, could modulate the formation of CYP450 enzymes.

The Applicant is currently conducting a clinical study (R668-AD-1433) designed to evaluate the effects of dupilumab on the PK of CYP substrates in subjects with AD. The primary objective of Study R668-AD-1433 is to evaluate the effects of repeated weekly SC doses of dupilumab on the in vivo activity of CYP3A, CYP2C19, CYP2C9, CYP1A2, and CYP2D6 by evaluating the PK of the respective CYP isoform-specific probe substrates midazolam, omeprazole, warfarin, caffeine, and metoprolol in subjects with moderate-to-severe AD before and after the treatment with dupilumab.
The agreed upon study is a study in AD patients and will evaluate the PK of CYP isoform-specific probe substrates before and after the treatment with dupilumab.

The Agency has reviewed the study protocol for the ongoing Study R668-AD-1433 under IND 107,969. The study design of this on-going study was found to be generally acceptable.

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

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 dupilumab alters the PK or metabolism of CYP substrates in AD patients treated with dupilumab.

(The ongoing DDI study is not to address the safe or effective use of dupilumab but to evaluate the potential impact of dupilumab treatment on the safe and effective use of the concomitant small molecule CYP substrate drugs which AD patients may 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)
PMR/PMC Development Template: Product Quality (CMC)

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

BLA #: BLA 761055/0
Product Name: Dupixent (dupilumab) Injection, 150 mg/mL

PMC Description: Revise the [b] CFU [b] mL bioburden limit for product sampled [b] mL after data from 10 additional drug product batches has been analyzed.

PMC Schedule Milestones: Final Report Submission: 12/2017

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

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

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

The data from 10 drug product batches during routine manufacturing will be trended to revise the current bioburden limit for [b] sampling point and this cannot be completed prior to BLA approval.

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

The current bioburden limit of [b] CFU [b] mL for the [b] mL bioburden limit should be revised based on the outcome from 10 drug product batches.
3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?
   Select only one. Fill out a new sheet for each type of PMR/PMC study.
   - Dissolution testing
   - Assay
   - Sterility
   - Potency
   - Product delivery
   - Drug substance characterization
   - Intermediates characterization
   - Impurity characterization
   - Reformulation
   - Manufacturing process issues
   - Other

   Describe the agreed-upon study:
   _____________________________________________________________________________________________________

5. To be completed by ONDQA/OBP Manager:
   - Does the study meet criteria for PMCs?
   - Are the objectives clear from the description of the PMC?
   - Has the applicant adequately justified the choice of schedule milestone dates?
   - Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

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

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

<table>
<thead>
<tr>
<th>BLA #</th>
<th>BLA 761055/0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Name:</td>
<td>Dupixent (dupilumab) Injection, 150 mg/mL</td>
</tr>
<tr>
<td>PMC Description:</td>
<td>Provide bioburden and sterility test qualification data from one additional batch of 150 mg/mL drug product. Submit the data in the first annual report.</td>
</tr>
</tbody>
</table>

**PMC Schedule Milestones:**

- **Final Report Submission (may include in the first annual report):** 05/2018

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

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

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

   The bioburden assay method qualification studies has been performed using samples from two drug product lots and sterility assay method qualification studies was completed using samples from two drug product lots. To demonstrate consistency, samples from three lots are required to complete the qualification study.

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

   The bioburden assay and sterility test method qualification studies have been conducted using samples from two lots of the drug product. The completion of this study will meet the qualification requirement of using samples from 3 lots of drug product.
3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

The sponsor will be performing the bioburden assay method qualification study for [Redacted] and for the sterility assay method qualification study for the drug product using an additional batch drug product and the data will be submitted in the first annual report.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

_______________________________________

The sponsor will [Redacted] performing the bioburden assay method qualification study for [Redacted] and for the sterility assay method qualification study for the drug product using an additional batch drug product and the data will be submitted in the first annual report.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW E WHITE
03/27/2017

TATIANA OUSSOVA
03/27/2017
I) RECOMMENDATION

The labels and labeling for Dupixent (dupilumab) Injection 300 mg/2 mL prefilled syringe submitted on the following dates are acceptable from a quality perspective:

- Prescribing Information: March 17, 2017
  \cdsesub1\evsprod\bla761055\0041\m1\us\114-labeling\114a-draft-label\proposed-pi.pdf

- Instructions for Use: March 17, 2017
  \cdsesub1\evsprod\bla761055\0041\m1\us\114-labeling\114a-draft-label\proposed-300mg-ifu-pfs-clean.pdf
  \cdsesub1\evsprod\bla761055\0041\m1\us\114-labeling\114a-draft-label\proposed-300mg-ifu-pfs-s-clean.pdf

- Patient Information: March 17, 2017
  \cdsesub1\evsprod\bla761055\0041\m1\us\114-labeling\114a-draft-label\proposed-ppi.pdf

- Container Labels: February 27, 2017
  \cdsesub1\evsprod\bla761055\0039\m1\us\114-labeling\114a-draft-label\s-dupi-crtn-300mgsyrbl.pdf
  \cdsesub1\evsprod\bla761055\0039\m1\us\114-labeling\114a-draft-label\300mg-pfs-s-syringe-container-label.pdf
II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted the final portion of the rolling submission for BLA 761055 Dupixent (dupilumab) on July 29, 2016. The Applicant submitted labeling on July 29, 2016 and updated labeling on November 1, 2016. This review evaluates the labeling submitted on November 1, 2016. Table 1 lists the proposed characteristics of Dupixent (dupilumab).

Table 1: Proposed Product Characteristics of Dupixent (dupilumab).

<table>
<thead>
<tr>
<th>Proprietary Name:</th>
<th>Dupixent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonproprietary Name:</td>
<td>dupilumab</td>
</tr>
<tr>
<td>Dosage Form:</td>
<td>Injection</td>
</tr>
<tr>
<td>Strength and Container-Closure:</td>
<td>300 mg/2 mL prefilled syringe</td>
</tr>
<tr>
<td>Route of Administration:</td>
<td>Subcutaneous injection</td>
</tr>
<tr>
<td>Storage and Handling:</td>
<td>Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. If necessary, pre-filled syringes may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days. Do not store above 77°F (25°C). After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded. Do not expose the syringe to heat or direct sunlight. Do NOT freeze. Do NOT expose to heat. Do NOT shake.</td>
</tr>
<tr>
<td>Indication:</td>
<td>Interleukin-4 receptor alpha antagonist indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.</td>
</tr>
<tr>
<td>Dose and Frequency:</td>
<td>Initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week.</td>
</tr>
</tbody>
</table>
III) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2: Materials Considered for this Label and Labeling Review

<table>
<thead>
<tr>
<th>Materials Reviewed</th>
<th>Appendix Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proposed Labels and Labeling</td>
<td>A</td>
</tr>
<tr>
<td>Other</td>
<td>B (n/a)</td>
</tr>
<tr>
<td>Relevant Code of Federal Regulations and CDER Labeling Best Practices</td>
<td>C</td>
</tr>
<tr>
<td>Acceptable Labels and Labeling</td>
<td>D</td>
</tr>
</tbody>
</table>

n/a = not applicable for this review

IV) DISCUSSION

The proposed labels were evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

V) CONCLUSION

The prescribing information, medication guide, patient labeling, instructions for use, container labels, and carton labeling for Proprietary Name (Established/Proper Name) dosage form, strength container closure 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 USP/NF 39/34. The labels and labeling submitted on the following dates are acceptable from a quality perspective:

- Prescribing Information: March 17, 2017
- Medication Guide: March 17, 2017
- Instructions for Use: March 17, 2017
- Patient Information: February 27, 2017
- Container Labels: February 27, 2017
- Carton Labeling: February 27, 2017
APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information
  \cdsesub{1}\evsprod\bla761055\0004\m1\us\114-labeling\114a-draft-label\s-dupi-uspi.pdf

- Instructions for Use
  \cdsesub{1}\evsprod\bla761055\0004\m1\us\114-labeling\114a-draft-label\s-dupi-ifu-300mgps.pdf
  \cdsesub{1}\evsprod\bla761055\0004\m1\us\114-labeling\114a-draft-label\s-dupi-ifu-300mgps-s.pdf

- Patient Information
  \cdsesub{1}\evsprod\bla761055\0004\m1\us\114-labeling\114a-draft-label\s-dupi-ppi.pdf

- Container Label
  \cdsesub{1}\evsprod\bla761055\0015\m1\us\114-labeling\114a-draft-label\s-dupi-crtn-300mgsyrlbl.pdf

- Carton Labeling
  \cdsesub{1}\evsprod\bla761055\0015\m1\us\114-labeling\114a-draft-label\s-dupi-crtn-300mgps.pdf
  \cdsesub{1}\evsprod\bla761055\0015\m1\us\114-labeling\114a-draft-label\s-dupi-crtn-300mgps-s.pdf

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page
Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

Table 3: Label\(^1\)\(^2\) and Labeling\(^3\) Standards

Container\(^4\) Label Evaluation

<table>
<thead>
<tr>
<th>Regulations</th>
<th>Comply</th>
<th>Comments and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>21 CFR 610.60 Container Label</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) <strong>Full label.</strong> The following items shall appear on the label affixed to the container of a product capable of bearing a full label:</td>
<td>x</td>
<td>We consider this a partial label. (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.</td>
</tr>
<tr>
<td>(b) <strong>Package label information</strong></td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(c) <strong>Partial label, proper name, lot, and manufacturer; individual dose for multiple dose containers; partial labels placed in a package with all items required for a package label</strong></td>
<td>x</td>
<td>To comply with 21 CFR 610.60(c), revise the manufacturer information to appear “Mfd by Regeneron Pharmaceuticals Inc.”&lt;br&gt;&lt;i&gt;The Applicant’s revision is acceptable.&lt;/i&gt; See DMEPA’s Human Factors, Label, Labeling, and Packaging Review regarding approval of the proper name as designated without a suffix.(^5)</td>
</tr>
<tr>
<td>(d) <strong>No container label</strong></td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(e) <strong>Visual inspection</strong></td>
<td>x</td>
<td>Conforms.</td>
</tr>
</tbody>
</table>

---

1 Per 21 CFR 1.3 (b) Label means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
2 Per CFR 600.3(dd) Label means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
3 Per 21 CFR 1.3(a) Labeling includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
4 Per 21 CFR 600.3(bb) Container (referred to also as “final container”) is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
<table>
<thead>
<tr>
<th>Regulations</th>
<th>Comply</th>
<th>Comments and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>21 CFR 201.1 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name and place of business of manufacturer, packer, or distributor</td>
<td>x</td>
<td>Does not apply to BLAs. See 21 CFR 610.60(c).</td>
</tr>
<tr>
<td><strong>21 CFR 201.2 Drugs and devices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDC numbers</td>
<td>x</td>
<td>Not required for partial labels per 21 CFR 610.60(c).</td>
</tr>
<tr>
<td><strong>21 CFR 201.5 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate directions for use</td>
<td>x</td>
<td>Not required for partial labels per 21 CFR 610.60(c).</td>
</tr>
<tr>
<td><strong>21 CFR 201.6 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misleading statements</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td><strong>21 CFR 201.10 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statement of ingredients</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td><strong>21 CFR 201.15 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prominence of required label statements</td>
<td>x</td>
<td>We consider the container label to be a partial label per 21 CFR 610.60(c). To improve readability of the total strength per total volume (300 mg/2 mL) on the partial label, remove (b) (4) The Applicant’s revision is acceptable.</td>
</tr>
<tr>
<td><strong>21 CFR 201.17 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of expiration date</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td><strong>21 CFR 201.25</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bar code label requirements</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td><strong>21 CFR 201.50 Statement of Identity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statement of identity</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td><strong>21 CFR 201.51 Declaration of net quantity of contents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declaration of net quantity</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td>Regulations</td>
<td>Comply</td>
<td>Comments and Recommendations</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>21 CFR 201.55 Statement of dosage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statement of dosage</td>
<td>x</td>
<td>Not required for partial labels per 21 CFR 610.60(c).</td>
</tr>
<tr>
<td><strong>21 CFR 201.100 Prescription drugs for human use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription drugs for human use</td>
<td>x</td>
<td>This information must appear on the carton, PI, and IFU.</td>
</tr>
</tbody>
</table>

Package Label Evaluation

<table>
<thead>
<tr>
<th>Regulations</th>
<th>Comply</th>
<th>Comments and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>21 CFR 610.61 Package Label</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| (a) Proper name | x | See DMEPA’s Human Factors, Label, Labeling, and Packaging Review regarding approval of the proper name as designated without a suffix.  

(b) Name, address, and license number of manufacturer | x | To comply with 21 CFR 610.61(b), revise the licensed manufacturer/Applicant to appear as "Manufactured by: Applicant on Form FDA 356h, Address, license number. For example: 

Manufactured by: 
Regeneron Pharmaceuticals, Inc. 
Tarrytown, NY 10591 
U.S. License No. 1760 
The Applicant’s revision is acceptable. |
| (c) Lot number or other lot identification | x | Conforms. |
| (d) Expiration date | x | Conforms. |

---

6 Per 21 CFR 600.3(cc) Package means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus this includes the carton, prescribing information, and patient labeling.

<table>
<thead>
<tr>
<th>Regulations</th>
<th>Comply</th>
<th>Comments and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(e) Preservative used and its concentration, if no preservative is use and the absence of a preservative is a safety factor, the words “no preservative”</strong></td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td><strong>(f) Number of containers, if more than one</strong></td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td><strong>(g) Amount of product in the container</strong></td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td><strong>(h) Recommended storage temperature</strong></td>
<td>x</td>
<td>Revise the carton labeling to include the instructions for storage outside the refrigerator and provide a place for patients/caregivers to write the date removed from the refrigerator. For example: Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do NOT freeze. Do NOT expose to heat or direct sunlight. Do NOT shake. If necessary, DUPIXENT may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days. Do not store above 77°F (25°C). After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded. Date removed from refrigerator <strong>/</strong>/___. The Applicant’s revision is acceptable.**</td>
</tr>
<tr>
<td><strong>(i) “Shake Well”, “Do not Freeze” or equivalent</strong></td>
<td>x</td>
<td>The labeling states “Do NOT freeze. Do NOT expose to heat. Do NOT shake.”</td>
</tr>
<tr>
<td>Regulations</td>
<td>Comply</td>
<td>Comments and Recommendations</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>(j) Recommended individual dose if multiple-dose container</td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(k) Route of administration</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td>(l) Known sensitizing substances</td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(m) Type and calculated amount of antibiotics added during manufacturing</td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(n) Inactive ingredients in case of safety factor</td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(o) Adjuvant, if present</td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(p) Source of the product when a factor in safe administration</td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(q) Identity of each microorganism used in manufacturing</td>
<td>x</td>
<td>Not applicable.</td>
</tr>
<tr>
<td>(r) Minimum potency of product expressed in terms of official standard of potency, or “No U.S. standard of potency”</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td>(s) “Rx only” statement for prescription biologicals</td>
<td>x</td>
<td>Conforms.</td>
</tr>
<tr>
<td>Regulations</td>
<td>Comply</td>
<td>Comments and Recommendations</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>21 CFR 610.62 Proper name; package label</strong>: Dupixent (dupilumab) is a monoclonal antibody, and thus a specified biologic per 21 CFR 601.2(a). Therefore, exempt from this CFR.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(a) Position: proper name</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>(b) Prominence</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>(c) Legible type</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 610.63 Divided Manufacturing</strong></td>
<td></td>
<td>Only one Applicant.</td>
</tr>
<tr>
<td>Divided manufacturing</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 610.64 Name and address of distributor</strong></td>
<td></td>
<td>See manufacturer comment above. The Applicant’s revision to manufacturer information is acceptable; therefore the proposed distributor information is acceptable.</td>
</tr>
<tr>
<td>Name and address may appear on the label provided the name, address, and license number of manufacturer appears on the label</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 610.67 Bar code</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bar code</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.2 Drugs and devices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NDC numbers</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.5 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adequate directions for use</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.6 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misleading statements</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.10 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statement of ingredients</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.15 Drugs</strong></td>
<td></td>
<td>Revise the strength statement to include a space between the number and the unit of measure (i.e. 300 mg/2 mL) to improve legibility. The Applicant’s revision is acceptable.</td>
</tr>
<tr>
<td>Prominence of required label statements</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 4072983
<table>
<thead>
<tr>
<th>Regulations</th>
<th>Comply</th>
<th>Comments and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>21 CFR 201.17 Drugs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location of expiration date</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.25</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bar code label requirements</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.50 Statement of identity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statement of identity</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.51 Declaration of net quantity of contents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declaration of net quantity</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.55 Statement of dosage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statement of dosage</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>21 CFR 201.100 Prescription drugs for human use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescription drugs for humans</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

Prescribing Information and Patient Labeling Evaluation

<table>
<thead>
<tr>
<th>Labeling Standards</th>
<th>Comply</th>
<th>Comments and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>PRESCRIBING INFORMATION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highlights of prescribing information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRODUCT TITLE 21 CFR 201.57(a)(2)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Full Prescribing Information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>3 DOSAGE FORMS AND STRENGTHS</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

All the required information appears in the proposed labeling. However, we revised the format to match...
<table>
<thead>
<tr>
<th>Labeling Standards</th>
<th>Comply</th>
<th>Comments and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 CFR 201.57(c)(4)</td>
<td></td>
<td>our best labeling practices.</td>
</tr>
<tr>
<td>6.2 IMMUNOGENICITY</td>
<td>x</td>
<td>DDDP relocated the standard paragraph regarding interpretation of immunogenicity studies to the beginning of this section.</td>
</tr>
<tr>
<td>11 DESCRIPTION 21 CFR 201.57(c)(12)</td>
<td>x</td>
<td>The product quality reviewer removed (b) (4) We revised the quantitative ingredient information (b) (4) to mg. We requested the applicant provide the amount of “sodium acetate” rather than “ ” The Applicant accepted our revisions.</td>
</tr>
<tr>
<td>16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)</td>
<td>x</td>
<td>We included the dosage forms “Injection” and identifying characteristics. The Applicant accepted our revisions.</td>
</tr>
</tbody>
</table>
| Manufacturer information For BLAs: 21 CFR 610.61, 21 CFR 610.64 For NDAs: 21 CFR 201.1 | | To comply with 21 CFR 610.61(b), revise the licensed manufacturer/Applicant to appear as “Manufactured by: Applicant on Form FDA 356h, Address, license number. For example: 
Manufactured by: 
Regeneron Pharmaceuticals, Inc. 
Tarrytown, NY 10591 
U.S. License No. 1760 
The Applicant accepted our revisions. |
<p>| MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION | | |
| Title (names and dosage form) | x | |
| Storage and Handling | x | We added the maximum temperature 77°F (25°C) allowed for “room temperature” storage and requested DMPP provide patient friendly language. The Applicant accepted our revisions. |
| Ingredients | x | |</p>
<table>
<thead>
<tr>
<th>Labeling Standards</th>
<th>Comply</th>
<th>Comments and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer Information For BLAs: 21 CFR 610.61, 21 CFR 610.64</td>
<td>x</td>
<td>To comply with 21 CFR 610.61(b), revise the licensed manufacturer/Applicant to appear as “Manufactured by: Applicant on Form FDA 356h, Address, license number. For example: Manufactured by: Regeneron Pharmaceuticals, Inc. Tarrytown, NY 10591 U.S. License No. 1760 The Applicant accepted our revisions.</td>
</tr>
</tbody>
</table>
APPENDIX D. Acceptable Labels and Labeling

- Prescribing Information
  \cdsesub1\evsprod\ bla761055\0041\m1\us\114-labeling\114a-draft-label\proposed-pi.pdf

- Instructions for Use
  \cdsesub1\evsprod\ bla761055\0041\m1\us\114-labeling\114a-draft-label\proposed-300mg-ifu-pfs-clean.pdf
  \cdsesub1\evsprod\ bla761055\0041\m1\us\114-labeling\114a-draft-label\proposed-300mg-ifu-pfs-s-clean.pdf

- Patient Information
  \cdsesub1\evsprod\ bla761055\0041\m1\us\114-labeling\114a-draft-label\proposed- ppi.pdf

- Container Labels
  \cdsesub1\evsprod\ bla761055\0039\m1\us\114-labeling\114a-draft-label\s-dupi-crtn-300mgsyrbl.pdf
  \cdsesub1\evsprod\ bla761055\0039\m1\us\114-labeling\114a-draft-label\300mg-pfs-s-syringe-container-label.pdf

- Carton Labeling
  \cdsesub1\evsprod\ bla761055\0039\m1\us\114-labeling\114a-draft-label\s-dupi-crtn-300mgpfs.pdf
  \cdsesub1\evsprod\ bla761055\0039\m1\us\114-labeling\114a-draft-label\s-dupi-crtn-300mgpfs-s.pdf

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JIBRIL ABDUS-SAMAD
03/22/2017

GUNther H BOEKHOUDT
03/22/2017
**HUMAN FACTORS, LABEL, LABELING, AND PACKAGING 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***

<table>
<thead>
<tr>
<th>Date of This Review:</th>
<th>March 10, 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requesting Office or Division:</td>
<td>Division of Dermatology and Dental Products (DDDP)</td>
</tr>
<tr>
<td>Application Type and Number:</td>
<td>BLA 761055</td>
</tr>
<tr>
<td>Product Name and Strength:</td>
<td>Dupixent (dupilumab) Injection 300 mg/2 mL (150 mg/mL) Prefilled Syringe (PFS)</td>
</tr>
<tr>
<td>Product Type:</td>
<td>Single Ingredient, Combination Product</td>
</tr>
<tr>
<td>Rx or OTC:</td>
<td>Rx</td>
</tr>
<tr>
<td>Applicant/Sponsor Name:</td>
<td>Regeneron Pharmaceuticals, Inc.</td>
</tr>
<tr>
<td>Submission Date:</td>
<td>July 29, 2016</td>
</tr>
<tr>
<td>OSE RCM #:</td>
<td>2016-1727 and 2016-2020</td>
</tr>
<tr>
<td>DMEPA Primary Reviewer:</td>
<td>Carlos M Mena-Grillasca, RPh</td>
</tr>
<tr>
<td>DMEPA Acting Associate Director:</td>
<td>Mishale Mistry, PharmD, MPH</td>
</tr>
<tr>
<td>DMEPA Associate Director for Human Factors:</td>
<td>QuynhNhu Nguyen, MS</td>
</tr>
<tr>
<td>OMEPRM Acting Deputy Director:</td>
<td>Lubna Merchant, MS, PharmD</td>
</tr>
</tbody>
</table>

Reference ID: 4067964
1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report, the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Dupixent (dupilumab) injection (BLA 761055), in response to consults from the Division of Dermatology and Dental Products (DDDP). The Applicant submitted BLA 761055, a 351(a) application, on July 29, 2016 for a prefilled syringe containing Dupixent (dupilumab), intended to treat moderate to severe atopic dermatitis. BLA 761055 was granted breakthrough therapy designation by the Agency.

2 MATERIALS REVIEWED

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

<table>
<thead>
<tr>
<th>Material Reviewed</th>
<th>Appendix Section (for Methods and Results)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Information/Prescribing Information</td>
<td>A</td>
</tr>
<tr>
<td>Previous DMEPA Reviews</td>
<td>B</td>
</tr>
<tr>
<td>Human Factors Study</td>
<td>C</td>
</tr>
<tr>
<td>ISMP Newsletters</td>
<td>D (N/A)</td>
</tr>
<tr>
<td>FDA Adverse Event Reporting System (FAERS)†</td>
<td>E (N/A)</td>
</tr>
<tr>
<td>Other</td>
<td>F (N/A)</td>
</tr>
<tr>
<td>Labels and Labeling</td>
<td>G</td>
</tr>
</tbody>
</table>

N/A=not applicable for this review
†We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The Applicant performed a HF validation study to evaluate the use of a standard, single dose, 2-mL pre-filled syringe (PFS) and a 2-mL pre-filled syringe with needle shield (PFS-S), the associated labels, labeling, packaging, and Instructions for Use (IFU) for Dupixent. The applicant submitted Human Factor validation protocols for review on September 14, 2015 and December 21, 2015. DMEPA provided comments to the HF validation protocols and the applicant implemented our recommendations prior to initiating the studies†.

On December 22, 2016, DMEPA submitted an Information Request (IR) letter to the applicant requesting clarification of their marketing plans for the PFS and PFS-S. On January 12, 2017, the applicant responded to the IR and indicated that they

Therefore, we note that there is a possibility that both pre-filled syringes be marketed simultaneously and we will recommend that the

---


applicant ensure that a single IFU, corresponding to the specific pre-filled syringe, is included in the carton.

A total of 201 participants participated in the Human Factors validation studies (n=104 for standard PFS; n=97 for PFS with needle shield). The study design included two trials: the 1st trial with IFU optional at the discretion of the participant and a 2nd trial with IFU mandatory in which the participant had to walk through the steps in the IFU.

The following table summarize the critical use-related errors.

<table>
<thead>
<tr>
<th>Task</th>
<th>PFS 1st trial: IFU optional</th>
<th>PFS 2nd trial: IFU mandatory</th>
<th>PFS-S 1st trial: IFU optional</th>
<th>PFS-S 2nd trial: IFU mandatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pinch the skin</td>
<td>27 errors (7 patients 16 caregivers 4 HCP)</td>
<td>6 errors (3 patients 3 caregivers 0 HCP)</td>
<td>51 errors (29 patients 18 caregivers 4 HCP)</td>
<td>16 errors (10 patients 6 caregivers 0 HCP)</td>
</tr>
<tr>
<td>Depress plunger</td>
<td>15 errors (6 patients 5 caregivers 4 HCP)</td>
<td>6 errors (3 patients 2 caregivers 1 HCP)</td>
<td>16 errors (7 patients 7 caregivers 2 HCP)</td>
<td>8 errors (4 patients 3 caregivers 1 HCP)</td>
</tr>
</tbody>
</table>

In term of the critical task errors observed, failure to pinch the skin and insert needle at 45° angle and failure to depress plunger and inject full dose:

- We agree with the applicant’s assessment that the errors relating to failure to pinch the skin and inject at 45° angle are would not result in patient harm. The need to pinch the skin and inject at a 45° angle is appropriate for patient with less body mass; and a 90° angle of injection is an acceptable injection technique for other products administered by subcutaneous injection. Finally, per the DDDP Medical Officer, there are no safety concerns associated with injecting at a 90° angle, but there may be a concern for diminished efficacy due to the potential for an intramuscular instead of subcutaneous injection.

Some participants misinterpreted the instruction to pinch the skin was only for the abdominal area and they were injecting into a pad at an injection site other than the stomach. They stated that it was difficult to determine if pinching the skin was necessary for all injection sites since the instruction reads “pinch a fold of skin at the injection site, as shown in the picture” and the picture only shows the stomach area.

Some participants indicated that the illustration did not clearly indicate how to insert the needle at a 45° angle. However, upon our review of the IFU, Step 9 shows the needle being inserted into the injection site at a 45° angle with a graphical depiction of the angle. Therefore, we do not find additional labeling changes are needed at this time.

The applicant did not propose further changes to the IFU to address these errors as such errors would not result in patient harm. Although DMEPA concurs with this residual risk, we determine that the instructions to pinch the skin can be improved in the IFU, based on the subjective feedback received in the study. After consulting with Patient Labeling, we provided the following revision to Step 8 of the IFU during labeling negotiations. The instruction was revised from “Pinch a fold of skin at the injection site (thigh or stomach, except 2 inches around your belly button, or outer area of the upper arm if injected by your caregiver). The figure below shows an example of pinching a fold of

Reference ID: 4067964 (b) (4)
skin on your stomach.” Revisions were made to clarify that end users should pinch the skin, regardless of the injection site.

- We also agree with the applicant’s assessment that difficulty depressing the plunger would not result in patient harm. We acknowledge that failure to deliver the full dose could result in decreased efficacy. However, it was observed within the study that these errors decreased in the second trial, which indicates that the users improved performance over time. In addition, since atopic dermatitis is a chronic condition and the product will be used over an extended period of time, we expect these errors to decrease with use.

Our evaluation of these errors indicated that they are associated with first time use of injectable products administered via PFS, or due to negative transfer from previous experience with PFS. In addition, the study results showed that most of these use errors did not reoccur as end users would detect and correct the error. Although the atopic dermatitis users would likely be naïve to the use of pre-filled syringes our evaluation of the risks associated with the use of the proposed product did not identify any new or unique risks for the proposed product. As such, we do not have any additional recommendations at this time to further mitigate the observed errors.

In addition, we noted multiple use-errors on non-essential tasks (e.g. checking expiration date, inspection the drug appearance, inspection for damage, choosing an injection site, clean injection site, washing hands). See Appendix C for more details. We note that similar errors occurred with the standard PFS and the PFS with needle shield (PFS-S). Also, the number of critical use errors decreased between the 1st trial (IFU optional) and 2nd trial (IFU mandatory), with the exception of “washing hands” (use errors increased between tasks but was deemed an artifact as participants did not feel they needed to re-wash their hands on the second attempt).

In addition to the HF validation study evaluation, our review of the proposed IFU did not identify any additional concerns from a medication errors perspective. Furthermore, our review of the proposed container label and carton labeling noted that the presentation of the strength statement can be improved to increase readability. As currently presented, there is no space between the numbers and the unit of measure (i.e. proposed 300mg/2mL vs. recommended 300 mg/2 mL). Also, there is inadequate contrast between the font color of the proper name and the background color of the label, which affects readability. Our recommendations in Section 4.1 to improve the container labels and carton labeling were sent to the Applicant on February 15, 2017 (Labeling PMR/PMC Discussion Comments communication). The applicant submitted revised labels and labeling on February 27, 2017, addressing our concerns (See Appendix G). We reviewed the revised labels and labeling submitted on February 27, 2017 and find them acceptable from a medication errors perspective.

Finally, we note that FDA recently issued a final guidance entitled Nonproprietary Naming of Biological Products on January 13, 2017 stating the Agency’s intention to designate proper names for certain biological products that include four-digit distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].

4 CONCLUSION & RECOMMENDATIONS

We find the Human Factors validation study results acceptable; however, we identified an area for improvement based on participant’s feedback regarding the instruction to pinch the skin. After
consulting with Patient Labeling we provided edits to the IFUs during labeling negotiations with the Applicant.

Our review of the proposed container labels and carton labeling identified areas for improvement with regards to the readability of the strength and proper name on the container labels and carton labeling of the proposed product. We provided recommendations for Regeneron Pharmaceuticals on February 15, 2017 in a Labeling PMR/PMC Discussion Comments communication. Regeneron submitted revised container labels and carton labeling on February 27, 2017, which we find acceptable. We have no additional recommendations at this time.

4.1 RECOMMENDATIONS FOR REGENERON PHARMACEUTICALS

A. Instructions for Use - Communicated to Applicant via Labeling Negotiations

1. We note that in your HF validation study, some participants stated that it was difficult to determine if pinching the skin was necessary for all injection sites since the instruction reads “Pinch a fold of skin at the injection site (thigh or stomach, except 2 inches around your belly button, or outer area of the upper arm if injected by your caregiver). The figure below shows an example of pinching a fold of skin on your stomach.” Therefore, we recommend revising Step 8 of the IFU to read:

“Pinch a fold of skin at the injection site (thigh or stomach, except 2 inches around your belly button, or outer area of the upper arm if injected by your caregiver). The figure below shows an example of pinching a fold of skin on your stomach.”

B. General Comments (All container labels and carton labeling) - Submitted to the Applicant on February 15, 2017 via Labeling PMR/PMC Discussion Comments communication

1. Revise the strength statement to include a space between the number and the unit of measure (i.e. 300 mg/2 mL) to improve legibility.

2. Revise the font color of the proper name to increase contrast with the background color to improve legibility. As currently presented the limited contrast between the font color and background color makes it difficult to read, especially considering the small size of the label and font on the container label.

3. As per your recent response to our Information Request letter, we note that you ensure that you only include the relevant IFU corresponding to the pre-filled syringe in the carton.
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION
Table 2 presents relevant product information for Dupixent that Regeneron Pharmaceuticals submitted on July 29, 2016.

<table>
<thead>
<tr>
<th>Table 2. Relevant Product Information for Dupixent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial Approval Date</strong></td>
</tr>
<tr>
<td><strong>Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td><strong>Route of Administration</strong></td>
</tr>
<tr>
<td><strong>Dosage Form</strong></td>
</tr>
<tr>
<td><strong>Strength</strong></td>
</tr>
<tr>
<td><strong>Dose and Frequency</strong></td>
</tr>
<tr>
<td><strong>How Supplied</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Storage</strong></td>
</tr>
<tr>
<td><strong>Container Closure</strong></td>
</tr>
</tbody>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods
On January 6, 2017 we searched the L:drive using the term, Dupixent and dupilumab, to identify reviews previously performed by DMEPA.

B.2 Results
Our search identified two previous relevant reviews\(^a\)\(^b\), and we confirmed that our previous recommendations were implemented or considered.


APPENDIX C. HUMAN FACTORS STUDY RESULTS

Standard PFS

8.1 PARTICIPANTS

A total of 104 participants participated in the HF validation study. The participants were representative of the intended users of the PFS, as described in Section 3.1. Table 6 shows the user groups that took part in the study and the tasks each group was asked to perform.

<table>
<thead>
<tr>
<th>User group (n = # of participants)</th>
<th>Description (n = # of participants)</th>
<th>Study tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe AD patients (n=38)</td>
<td>Injection-naive (n=23)</td>
<td>x x x</td>
</tr>
<tr>
<td></td>
<td>Experienced in self-injection with a syringe (n=15)</td>
<td>x x x</td>
</tr>
<tr>
<td>Non-professional (layperson) caregivers (n=38), caring for patients with chronic diseases&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Injection-naive (n=15)</td>
<td>x x x</td>
</tr>
<tr>
<td></td>
<td>Experienced in injection with a syringe (n=21)</td>
<td>x x x</td>
</tr>
<tr>
<td>Nurses currently administering/training AD patients (n=15)</td>
<td>Syringe-experienced</td>
<td>x x x</td>
</tr>
<tr>
<td>Pharmacists (n=15)</td>
<td>Pharmacists</td>
<td>x - -</td>
</tr>
</tbody>
</table>

<sup>a</sup> Recruiting was opened to include all lay caregivers of someone with a chronic illness, to fulfill the quota of caregivers (this deviated from the original protocol). The following participants did not care for someone with AD, but another chronic illness: n=17 (C11, C14, C15, C16, C17, C18, C19, C22, C23, C24, C25, C26, C27, C29, C30, C31, and C32).

Table 7 - Patient participant gender and age

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD population</td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td>Study patient population</td>
<td>79%</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>18 to 29</th>
<th>30 to 39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD population</td>
<td>~27%</td>
<td>~27%</td>
<td>~20%</td>
<td>~13%</td>
<td>~8%</td>
<td>~5%</td>
</tr>
<tr>
<td>Study patient population</td>
<td>3</td>
<td>4</td>
<td>13</td>
<td>12</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 8 - Patient participants' AD severity based on POEM score (day of test session)

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>17 (45%)</td>
<td>15 (39%)</td>
<td>6 (16%)</td>
</tr>
</tbody>
</table>
Table 9 and Table 10 show the literacy levels of participants recruited for the HF validation studies.

### Table 9 - Scores and grade equivalents for the REALM-SF

<table>
<thead>
<tr>
<th>REALM score</th>
<th>0</th>
<th>1-3</th>
<th>4-6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade range</td>
<td>Third grade and below; will not be able to read most low-literacy materials; will need repeated oral instructions; materials composed primarily of illustrations, or audio or video tapes</td>
<td>Fourth to sixth grade; will need low-literacy materials, may not be able to read prescription labels</td>
<td>Seventh to eighth grade; will struggle with most patient education materials; will not be offended by low-literacy materials</td>
<td>High school, will be able to read most patient education materials</td>
</tr>
</tbody>
</table>

REALM score distribution of study population subset that was assessed prior to participation (n=69)  
1% 0% 22% 77%

### Table 10 - Patient and caregiver participant's literacy assessment

<table>
<thead>
<tr>
<th>STOFHLA scoring range and literacy category</th>
<th>(0-15) Below basic</th>
<th>(16-18) Basic</th>
<th>(19-24) Intermediate</th>
<th>(25-36) Proficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literacy grade</td>
<td>Indicates no more than the most simple and concrete literacy skills.</td>
<td>Indicates skills necessary to perform simple and everyday literacy activities.</td>
<td>Indicates skills necessary to perform moderately challenging literacy activities.</td>
<td>Indicates skills necessary to perform more complex and challenging literacy activities.</td>
</tr>
<tr>
<td>Study patient and caregiver population (n=71)</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
<td>98%</td>
</tr>
<tr>
<td>US population (11)</td>
<td>14%</td>
<td>22%</td>
<td>52%</td>
<td>14%</td>
</tr>
</tbody>
</table>

During the first handling task session, all participants were provided with the IFU. They were allowed, but not instructed or required, to use the IFU at any point in the study session if they chose. In accordance with agency review comments to the study protocol (2), all participants were instructed to read and follow the IFU in every step of the procedure in a second handling task that constituted an observational IFU assessment (related to handling tasks).

Another study task was related to safety-relevant information in the IFU (Appendix 1) and involved review of the IFU content with participants who were asked to find answers to a set of questions.

Finally two study tasks were related to differentiating the product's primary and secondary packaging from a set of comparator items (Appendix 6). The period between the introduction to the product package and the device and the package and device differentiation tasks provided adequate decay, particularly because the participants performed other tasks in the meantime.
### Table 11 - Use errors recorded during handling sub-tasks in task 1 (IFU optional) and task 2 (IFU mandatory)

<table>
<thead>
<tr>
<th>Step</th>
<th>Critical task?</th>
<th>Use errors during task 1 (IFU optional, n=104)</th>
<th>Use errors during task 2 (IFU mandatory, n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Yes</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2.2</td>
<td>Yes</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>2.4</td>
<td>Yes</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>2.5</td>
<td>No</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2.7</td>
<td>Yes</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>3.1</td>
<td>Yes</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>3.2</td>
<td>Yes</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>3.3</td>
<td>Yes</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>3.4</td>
<td>Yes</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>4.0</td>
<td>Yes</td>
<td>35</td>
<td>6</td>
</tr>
</tbody>
</table>

### PFS with Safety Shield

#### 7.3 PARTICIPANTS

A total of 97 participants participated in the HF validation study. The participants were representative of the intended users of the PFS-S, as described in Section 3.1. Table 6 shows the user groups that took part in the study and the tasks each group was asked to perform.

### Table 6 - Participants involved in the HF validation study

<table>
<thead>
<tr>
<th>User group</th>
<th>Description</th>
<th>Study tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe AD patients (n=34)</td>
<td>Injection-naive (n=19)</td>
<td>Handling x x x</td>
</tr>
<tr>
<td></td>
<td>Experienced in self-injection with a syringe (n=15)</td>
<td></td>
</tr>
<tr>
<td>Non-professional (layperson) caregivers (n=33), caring for patients with chronic diseases*a</td>
<td>Injection-naive (n=15)</td>
<td>Handling x x x</td>
</tr>
<tr>
<td></td>
<td>Experienced in injection with a syringe (n=18)</td>
<td></td>
</tr>
<tr>
<td>Nurses currently administering/training AD patients (n=15)</td>
<td>Syringe-experienced</td>
<td>Handling x x x</td>
</tr>
<tr>
<td>Pharmacists (n=15)</td>
<td>Pharmacists</td>
<td>Handling x</td>
</tr>
</tbody>
</table>

*a Recruiting was opened to include all lay caregivers of someone with a chronic illness, to fulfill the quota of caregivers (this deviated from the original protocol). The following participants did not care for someone with AD, but another chronic illness: n=17 (C11, C14, C15, C16, C17, C18, C19, C22, C23, C24, C25, C26, C27, C29, C30, C31, and C32).

Reference ID: 4067964
Table 7 - Patient participant gender and age

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD population</td>
<td>56%</td>
<td>44%</td>
</tr>
<tr>
<td>Study patient population</td>
<td>74%</td>
<td>26%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>18 to 20</th>
<th>30 to 39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD population</td>
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<td>~27%</td>
<td>~20%</td>
<td>~13%</td>
<td>~8%</td>
<td>~5%</td>
</tr>
<tr>
<td>Study patient population</td>
<td>4</td>
<td>8</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 8 - Patient participants' AD severity based on POEM score (day of test session)

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 (17%)</td>
<td>17 (50%)</td>
<td>11 (33%)</td>
</tr>
</tbody>
</table>

Table 9 - Scores and grade equivalents for the REALM-SF

<table>
<thead>
<tr>
<th>REALM score</th>
<th>0</th>
<th>1-3</th>
<th>4-6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade range</td>
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<td>Fourth to sixth grade; will need low-literacy material, may not be able to read prescription labels.</td>
<td>Seventh to eighth grade; will struggle with most patient education materials; not be offended by low-literacy materials.</td>
<td>High school; will be able to read most patient education materials.</td>
</tr>
<tr>
<td>REALM score distribution of study population subset that was assessed prior to participation (n=23)</td>
<td>4%</td>
<td>4%</td>
<td>31%</td>
<td>51%</td>
</tr>
</tbody>
</table>

Table 10 - Patient and caregiver participant’s literacy assessment

<table>
<thead>
<tr>
<th>STOFHLA scoring range and literacy category</th>
<th>(0-15) Below basic</th>
<th>(16-18) Basic</th>
<th>(19-24) Intermediate</th>
<th>(25-36) Proficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literacy grade</td>
<td>Indicates no more than the most simple and concrete literacy skills.</td>
<td>Indicates skills necessary to perform simple and everyday literacy activities.</td>
<td>Indicates skills necessary to perform moderately challenging literacy activities.</td>
<td>Indicates skills necessary to perform more complex and challenging literacy activities.</td>
</tr>
<tr>
<td>Study patient and caregiver population (n=67)</td>
<td>(0)</td>
<td>(0)</td>
<td>(7)</td>
<td>(60)</td>
</tr>
<tr>
<td>US population (11)</td>
<td>14%</td>
<td>22%</td>
<td>52%</td>
<td>14%</td>
</tr>
</tbody>
</table>
During the first handling task session, all participants were provided with the IFU. They were allowed, but not instructed or required, to use the IFU at any point in the study session if they chose. In accordance with agency review comments to the study protocol (2), all participants were instructed to read and follow the IFU before performing every step of the procedure. This second handling task constituted explicit validation of the IFU.

Another study task was related to safety-relevant information in the IFU (Appendix 1) and involved review of the IFU content with participants who were asked to find answers to a set of questions.

Finally two study tasks were related to differentiating the product’s primary and secondary packaging from a set of comparator items (Appendix 6). The period between the introduction to the product package and the device and the package and device differentiation tasks provided adequate decay, particularly because the participants performed other tasks in the meantime.

<table>
<thead>
<tr>
<th>Sub-task</th>
<th>Step</th>
<th>Critical task?</th>
<th>Use errors during task 1 (IFU optional, n=82)</th>
<th>Use errors during task 2 (IFU mandatory, n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Open the PFS-S carton</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.2</td>
<td>Remove the syringe from the carton</td>
<td>Yes</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2.3</td>
<td>Check the expiration date on the PFS-S box and/or the syringe label</td>
<td>Yes</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>2.4</td>
<td>Check the drug integrity (ie, color, clarity, particles)</td>
<td>Yes</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>2.6</td>
<td>Choose an appropriate injection site</td>
<td>No</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>2.7</td>
<td>Wash hands/Clean the injection site</td>
<td>Yes</td>
<td>10</td>
<td>16a</td>
</tr>
<tr>
<td>3.1</td>
<td>Remove the needle cap</td>
<td>Yes</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>3.2</td>
<td>Pinch the skin and insert the needle into the injection site at a 45-degree angle</td>
<td>Yes</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>3.3</td>
<td>Depress the plunger/Inject full dose/Activate safety system</td>
<td>Yes</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>3.4</td>
<td>Remove the needle from the skin at the angle of insertion</td>
<td>Yes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>4.1</td>
<td>Discard the PFS-S into the sharps container</td>
<td>No</td>
<td>15</td>
<td>3</td>
</tr>
</tbody>
</table>

*a The increase in use errors for disinfection between task 1 and task 2 is largely due to the artificial study situation and to some degree to the fact that participants did not feel they needed to re-wash their hands if they had done it as part of task 1. Some participants, however, reported that they had followed the IFU and had not seen instructions to wash hands. See task 2.7 below in Table 16 for a more detailed discussion.

Summary of Critical Task Errors

**Failure to pinch the skin and insert needle at 45° angle:**

- **PFS:** In general, participants either did not read the IFU, forgot to pinch the skin, relied on previous experience or from watching HCP administer injections, or a study artifact due to the use of injection pads.
- **PFS-S:** In general, participants either did not read the IFU, forgot to pinch the skin, relied on previous experience or from watching HCP administer injections, or a study artifact due to the use of injection pads. In addition, some participants indicated that they would not pinch the skin for injection into the
arm. Finally, some participants did not inject at a 45° angle because they did not know what angle/position that was, felt more comfortable injecting at a 90° angle, were taught to inject at a 90° angle, or that is how they saw their doctors injecting.

Failure to depress plunger and inject full dose:

- **PFS:**
  - Seven participants had difficulty while depressing the plunger to complete the injection and indicated that the resistance they felt while depressing the plunger was higher than expected. Of note, end users will administer 2 mL volume subcutaneously, which is a larger amount than what is typical of prefilled syringes for subcutaneous injection. Hence, due to the volume, it is expected that more force is required to depress the plunger.
  - One participant administered both syringes included in the carton during both the first and second injections. This was deemed a study artifact as the patient stated that in real life she would follow the medication orders she receives.
  - One participant injected a partial dose (approximately 90%) and another participant inserted the needle and removed her hand from the syringe to turn over the IFU and left the needle dangling in the skin. Both cases are deemed study artifacts as the use-errors occurred while the participants were trying to turn over the IFU while administering the injection. Both participants stated that in real life they would not have interrupted the injection to turn the IFU.
  - One injection experienced participant initially pulled back on the plunger prior to injecting and then pushed the plunger down to inject the medication. The participant indicated that this was a standard procedure when she previously gave herself injections.
  - Five injection experienced participants primed the syringe before injecting. Four participants indicated that it was normal procedure to prime the needle before injecting. The fifth participant indicated that the presence of bubbles in the syringe confused her as it is a common procedure to remove air bubbles from syringes before injecting into her patients. One participant injected approximately 95% of the medication in the syringe during the first injection. She thought she injected the full dose. She experienced considerable resistance when depressing the plunger. The second injection was completed successfully.

- **PFS-S:**
  - Seven participants had difficulty depressing the plunger to complete the injection. Four participants indicated that the resistance they felt while depressing the plunger was higher than expected. Two participants were administering the injection in an awkward body posture. One participant had trembling in his/her hands due to sciatica condition.
  - One participant injected about half the contents of the syringe on the first attempt. She did not read the IFU and indicated that injecting the entire contents of the syringe would be “putting too much in [her] body”. After reading the IFU, she administered the complete dose successfully.
  - Two participants primed the syringe before inserting the needle. One participant stated that she would always prime the syringe to remove bubbles despite the IFU stating that air bubbles are ok. The second participant stated that he/she has watched nurses prime syringes and believed this was a common practice.
  - One participant did not complete the injection due to difficulty trying to self inject into the upper arm. This was an injection-naive patient that reported being nervous before his/her first injection. During the second injection the participant administered the complete dose successfully.
  - Some participants did not fully depressed the plunger, and as a result the safety system did not activate after removing the needle from the skin. Causes for these use-errors provided by the applicant include study artifact (i.e. positioning of the mannequin and IFU laid out on the table), previous experience pulling the plunger back before pressing forward, worried about pressing too
hard, nervousness, not referencing the IFU, righthanded participant using the left hand for the injection, not being aware of the safety system, increased resistance, etc. During the second injection, most of the participants administered the complete dose successfully.

APPENDIX D.  ISMP NEWSLETTERS

N/A

APPENDIX E.  FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F.  OTHER

N/A
APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed
Using the principles of human factors and Failure Mode and Effects Analysis, along with postmarket medication error data, we reviewed the following Dupixent labels and labeling submitted by Regeneron Pharmaceuticals on November 1, 2016 and revised labels and labeling submitted on February 27, 2017.

- Container label
- Carton labeling
- Prescribing Information (not pictured)
- Instructions for Use (not pictured)

G.2 Label and Labeling Images (not to scale)

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
03/10/2017

MISHALE P MISTRY
03/10/2017

QUYNH NHU T NGUYEN
03/10/2017

LUBNA A MERCHANT
03/10/2017
Clinical Inspection Summary

Date: February 13, 2017

From
Roy Blay, Ph.D., Reviewer
Janice K. Pohlman, M.D., M.P.H., Team Leader
Kassa Ayalew, M.D., M.P.H., Branch Chief,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

To
Matthew White\Project Manager
Brenda Carr\Medical Officer
Snezana Trajkovic\Team Leader
Division of Dermatologic and Dental Products

NDA/BLA #: BLA 761055
Applicant: Regeneron Pharmaceuticals, Inc.

Drug: Dupilumab
NME (Yes/No): Yes
Therapeutic Classification: Priority Review

Proposed Indication(s): Treatment of atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy, or not advisable.

Consultation Request Date: August 24, 2016
Summary Goal Date: February 17, 2017
Action Goal Date: March 17, 2017
PDUFA Date: March 29, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Sofen, Brüning, and Kolodziej were inspected in support of this NDA. In addition, the sponsor, Regeneron Pharmaceuticals, Inc., was also inspected. The final classification of the inspections of Drs. Sofen and Kolodziej was No Action Indicated (NAI), and the final classification of the inspection of Dr. Brüning was Voluntary Action Indicated (VAI). The final classification of the inspection of the sponsor, Regeneron, was NAI.

Based on the results of the clinical investigator and sponsor inspections, the studies of Drs. Sofen, Brüning, and Kolodziej appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.
2. BACKGROUND

The Applicant submitted this BLA to support the use of dupilumab in the treatment of atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy, or not advisable.

The following three protocols were inspected in support of this application:

R668-AD-1334 and R668-AD-1416 entitled “A Phase 3 Confirmatory Study Investigating the Efficacy and Safety of Dupilumab Monotherapy Administered to Adult Patients with Moderate-to-Severe Atopic Dermatitis, and

R668-AD-1224 entitled “A Randomized, Double-Blind, Placebo-Controlled Study to Demonstrate the Efficacy and Long-Term Safety of Dupilumab in Adult Patients with Moderate-to-Severe Atopic Dermatitis”.

Protocols R668-AD-1334 and R668-AD-1416

The primary objective of these identical studies was to demonstrate the efficacy of dupilumab monotherapy compared to placebo treatment in adult patients with moderate-to-severe atopic dermatitis (AD). These were randomized, double-blind, placebo-controlled, parallel group studies which randomized subjects in a 1:1:1 ratio to receive once weekly ( qw) SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1, every 2 weeks ( q2w), SC injections of 300 mg dupilumab following a loading dose of 600 mg on day 1 ( during weeks in which dupilumab was not administered, patients received placebo), or matching placebo.

The primary efficacy endpoint in the US was the proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16. For the European Union and Japan, the co-primary endpoints were the proportion of patients with EASI-75 (≥75% improvement from baseline) at Week 16 and the proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16.

Protocol R668-AD-1334 was conducted at 138 clinical sites in 10 countries. There were 671 subjects analyzed in total for this study. The sponsor concluded that dupilumab dose regimens of 300 mg Q2W and 300 mg QW, administered as monotherapy for 16 weeks, provide substantial and sustained clinical benefits to patients with moderate to severe AD inadequately controlled with topical medications.

Protocol R668-AD-1416 was conducted at 136 clinical sites in ten countries. There were 708 subjects analyzed in total for this study. The sponsor concluded that dupilumab dose regimens of 300 mg Q2W and 300 mg QW, administered as monotherapy for 16 weeks, provide substantial and sustained clinical benefits to patients with moderate to severe AD inadequately controlled with topical medications.
Protocol R668-AD-1224

The primary objective of the study was to demonstrate the efficacy of dupilumab administered concomitantly with topical corticosteroids (TCS) through Week 16 in adult patients with moderate-to-severe atopic dermatitis (AD) compared to placebo administered concomitantly with TCS. A secondary objective of the study was to evaluate the long-term safety of dupilumab when administered concomitantly with TCS for up to 52 weeks. This was a Phase 3, randomized, double-blind, placebo-controlled study which randomized subjects in a 3:1:3 ratio to receive weekly (QW) or every 2 weeks (Q2W) subcutaneous (SC) injections of 300 mg dupilumab, following a loading dose of 600 mg on Day 1 (during weeks in which dupilumab was not administered, patients received placebo), or matching placebo.

The primary efficacy endpoint in the US was the proportion of subjects with both IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16. For the European Union countries and Japan the co-primary endpoints were the proportion of patients with Eczema Area andSeverity Index (EASI)-75 (≥75% improvement from baseline) at Week 16 and the proportion of patients with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16.

Protocol R668-AD-1224 was conducted at 162 clinical sites in 14 countries. There were 740 subjects analyzed in total for this study. The sponsor concluded that dupilumab dose regimens of 300 mg Q2W and 300 mg QW, administered concomitantly with TCS for up to 52 weeks) provide substantial and sustained clinical benefits to patients with moderate-to-severe AD inadequately controlled with medium or higher potency topical medications.

Drs. Sofen’s, Brüning’s, and Kolodziej’s sites were selected for inspection because of their respective enrollments of relatively large numbers of subjects.
3. RESULTS (by site):

<table>
<thead>
<tr>
<th>Site #/ Name of CI/ Address</th>
<th>Protocol #/ # of Subjects (enrolled)</th>
<th>Inspection Dates</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>840004/ Sofen, Howard 8930 S Sepulveda Blvd #114 Los Angeles, CA 90045</td>
<td>R668-AD-1334/ 28</td>
<td>7-15 Nov 2016</td>
<td>NAI</td>
</tr>
<tr>
<td>276007/ Brüning, Harald Schönberger Str. 72-74 Kiel, Schleswig-Holstein 24148 Germany</td>
<td>R668-AD-1416/ 13</td>
<td>12-16 Dec 2016</td>
<td>VAI</td>
</tr>
<tr>
<td>616025/ Kolodziej, Tomasz ul. Swobodna 8A Wroclaw, Dolnoslaskie 50-088 Poland</td>
<td>R668-AD-1224/ 14</td>
<td>5-9 Dec 2016</td>
<td>NAI</td>
</tr>
<tr>
<td>Regeneron Pharmaceuticals, Inc. 77 Old Saw Mill River Road Tarrytown, NY 10591 (sponsor)</td>
<td>R668-AD-1334/ R668-AD-1416/ R668-AD-1224/</td>
<td>28-30 Nov 2016</td>
<td>NAI</td>
</tr>
</tbody>
</table>

Key to Compliance 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 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Howard Sofen, M.D.

At this site for Protocol # R668-AD-1334, 31 subjects were screened and 28 subjects were randomized to the study. Three subjects failed screening with one withdrawing consent and two failing to meet inclusion/exclusion criteria.
All of the informed consent forms that were reviewed were signed prior to the initiation of any screening procedures. Data generated on site was reported to the sponsor via electronic Case Report Forms (eCRFs). Record review included, but was not limited to, financial disclosure, protocol deviations, sponsor, monitor, and IRB communications, adverse events, medical histories, laboratory reports, study visits, concomitant medications, progress notes, and test article control.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Harald Brüning, M.D.

At this site for Protocol # R668-AD-1416, 13 subjects were screened, enrolled, and completed the study.

The informed consent forms (ICFs) for 12 of the 13 subjects in the study were reviewed during the inspection (the ICF for Subject 005 was missing). The reviewed ICFs were signed prior to the initiation of any screening procedures. The study records of all 13 subjects were reviewed. Record review included, but was not limited to, Form FDA 1572s, financial disclosure forms, monitoring documentation, blinding/randomization, primary efficacy data, adverse events, subject discontinuations, and test article accountability and storage. Protocol deviations were compared between the source documents and the electronic Case Report Forms (eCRFs)

A Form FDA 483 was issued at the conclusion of the inspection noting improper documentation of informed consent. Observations included the absence of the signed informed consent form for Subject 005 (the ICF was missing during the inspection but a copy of the signed consent form was provided by the clinical investigator in his written response to the observation on the Form FDA 483), a consent form for the pharmacogenomics sub-study that was signed by Subject 004 on May 27, 2015, even though samples were collected from the subject on May 6, 2015, and the back-dating of an informed consent form by Subject 008 on May 28, 2015, though the actual date of signature was June 4, 2015. These observations were acknowledged by Dr. Brüning in his written response dated December 23, 2016, in which he committed to the implementation of new procedures to ensure proper handling of consent forms.

Notwithstanding the deficiencies regarding informed consent as noted above which would not appear to significantly affect either subject safety or efficacy considerations, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.
3. **Tomasz Kolodziej, M.D.**

At this site for Protocol R668-AD-1224, 14 subjects were screened and randomized to the study.

The informed consent forms for all 14 randomized subjects were reviewed. All subjects signed the consent forms prior to any study-related procedures. Two subjects withdrew from the study as reported. The records of 11 subjects were reviewed in detail.

Source documents were compared with Case Report Forms (CRFs) and line listings. Records reviewed included, but were not limited to, training, eligibility criteria, financial disclosure, screening and enrollment, laboratory testing, adverse events, concomitant therapies, randomization, electronic Case Report Forms (eCRFs), primary and secondary efficacy endpoints, sponsor and monitor correspondence, delegation of authority, and drug accountability and storage.

A Form FDA 483 was not issued at the conclusion of the inspection. This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. **Regeneron Pharmaceuticals, Inc.**

The inspection audited Protocols R668-AD-1334, R668-AD-1416, and R668-AD-1224 and focused on the following clinical investigators: Drs. Sofen, Brüning, and Kolodziej.

The inspection reviewed the following records which included, but were not limited to, monitoring plans, contracts, transfers of obligations, monitoring reports, safety and data management plans and related SOPs, oversight records, 1572s, training, and study drug records. Also reviewed was verification of primary end point data, monitoring, review of controls and security of electronic systems, and data collection and handling procedures.

A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection. The studies appear to have been conducted adequately, and the data submitted by the sponsor may be used 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}

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

CONCURRENCE:

{See appended electronic signature page}

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

CC:
Central Doc. Rm. BLA 761055
DDDP\Division Director\Kendall Marcus
DDDP\Team Leader\Snezana Trajkovic
DDDP\Medical Officer\Brenda Carr
DDDP\Project Manager\Matthew White
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Janice Pohlman
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters
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/s/

ROY A BLAY
02/14/2017

JANICE K POHLMAN
02/14/2017

KASSA AYALEW
02/14/2017
Date: 1/27/2017

From: Sapana Patel, PharmD.
Pharmacist
General Hospital Devices Branch/DAGRID/ODE/CDRH

To: Matthew White
Regulatory Health Project Manager
CDER/OND/ODE III/ DDDP

Subject: BLA 761055 Memo/ICC1600482

Recommendation:
Approval of the Device Constituent

<table>
<thead>
<tr>
<th>Applicant</th>
<th>Regeneron Pharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication for Use</td>
<td>Treatment of atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy. or not advisable.</td>
</tr>
<tr>
<td>Drug / Biologic Constituent</td>
<td>Dupilumab</td>
</tr>
<tr>
<td>Device Constituent</td>
<td>Prefilled syringe with needle safety system</td>
</tr>
</tbody>
</table>

Digital Signature Concurrency Table

<table>
<thead>
<tr>
<th>Reviewer Sign-Off</th>
<th>Sapana Patel -S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branch Sign-Off</td>
<td>Alan M. Stevens -S</td>
</tr>
</tbody>
</table>

Reference ID: 4049659
1. PURPOSE/BACKGROUND

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA BLA 761055. Regeneron Pharmaceuticals is submitting a Biologics License Application (BLA) for Dupilumab, a recombinant human IgG4 monoclonal antibody for the treatment of atopic dermatitis in adult patients whose disease is not adequately controlled with topical prescription therapy or not advisable. The device constituent is a prefilled syringe with needle safety system. CDER requests a CDRH device component evaluation.

The primary container closure, prefilled syringe, contains all drug contacting components; therefore review of biocompatibility and sterility of the glass barrel, needle, plunger stopper and rigid needle shield deferred to CDER.

The device for BLA 761055 includes the following device constituent parts:

<table>
<thead>
<tr>
<th>Packaging components</th>
<th>Plunger rod</th>
<th>Finger flange</th>
<th>Safety system</th>
<th>Plunger stopper</th>
<th>Syringe barrel + staked needle + rigid needle shield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illustration of packaging component</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supplier name</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
<td>(b) (4)</td>
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DMF reference number

<table>
<thead>
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<th>Document Title</th>
<th>Date-version</th>
<th>Location</th>
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<td>6/29/2016</td>
<td>Sequence 0003</td>
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<tr>
<td>BLA 761055</td>
<td>7/29/2016</td>
<td>Sequence 0004</td>
</tr>
<tr>
<td>QUA-000966-0002</td>
<td>6/17/2016</td>
<td>Sequence 0004</td>
</tr>
</tbody>
</table>

3. DEVICE DESCRIPTION (located in Section 3.2.P.2.4)
The dupilumab PFS-S presentation is supplied in a ready to use, sterile, single dose (no partial dosing), and prefilled and disposable glass syringe assembled with a plunger rod and inserted within a safety system preassembled with a finger flange.

![Dupilumab PFS-S Presentation](image)

**Figure 1:** Prefilled syringe assembled with safety system, containing 150 mg/mL dupilumab solution for injection. The label affixed to the syringe in the figure above is a mock-up of the actual label to be affixed to the commercial syringe. The product’s proprietary name has not been finalized and is for illustration purposes only.

**Intended User/Population:**
Adult population

**Prefilled Syringe:**

- A 2.25 mL clear glass syringe barrel equipped with a 27 Gauge (G) ½” (inch) staked needle, protected by a rigid needle shield (RNS) composed of an
- A plunger stopper

The syringes with rigid needle shield are composed of the following materials of construction described in the Table 1.

<table>
<thead>
<tr>
<th>Component part</th>
<th>Material/Type</th>
<th>Color</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syringe (2.25 mL)</td>
<td>Clear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staked needle</td>
<td>Steel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid Needle Shield (RNS)</td>
<td>Grey</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transparent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 4049659
The syringes are tested and delivered ready to use for filling \((b)(4)\) accompanied by a certificate of conformity.

The dimensions of the barrel meet requirements of ISO 11040-4 Prefilled Syringes Part 4: Glass Barrel for Injectable for a 2.25 mL volume barrel.

<table>
<thead>
<tr>
<th>Table 7 - ISO 11040-4 glass barrel dimensions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISO 11040-4 dimensions</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Glass barrel</td>
</tr>
<tr>
<td>d1</td>
</tr>
<tr>
<td>d2</td>
</tr>
<tr>
<td>d3</td>
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<tr>
<td>l1</td>
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<td>e</td>
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<td>a</td>
</tr>
<tr>
<td>b</td>
</tr>
<tr>
<td>c</td>
</tr>
</tbody>
</table>

The composition of the plunger stopper is detailed in Table 2.

<table>
<thead>
<tr>
<th>Table 2 - Description of the plunger stopper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Component part</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Plunger stopper</td>
</tr>
</tbody>
</table>

The dimensions of the needle meet requirements of ISO 11040-4 Prefilled Syringes Part 4: Glass Barrel for Injectable (ISO 7864).
Table 8 - ISO 11040-4 needle dimensions

<table>
<thead>
<tr>
<th>ISO 11040-4 dimensions (ISO 7864 and ISO 9626)</th>
<th>Dupilumab 2.25 mL syringe dimensions (mm)</th>
<th>Acceptance criteria</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needle external diameter</td>
<td>(b)(4)</td>
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<td>Compiles</td>
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<tr>
<td>Needle internal diameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum deflection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needle length</td>
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<td></td>
<td></td>
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<tr>
<td>Primary bevel length</td>
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<tr>
<td>Secondary bevel length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Facet angle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needle lumen patency</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Plunger stoppers are tested and delivered ready to use for filling (b)(4) by the supplier accompanied by a certificate of conformity.

Quality control tests of syringes are performed by subcontractors or by Sanofi. Incoming controls are performed on every batch received using sampling per ISO 2859-1. The sponsor has provided drawings, specifications and a list of controls performed on the prefilled syringe and plunger stopper in Section 3.2. P.2.7.

Safety System
The bulk prefilled syringe is assembled with an (b)(4) plunger rod to allow delivery of the drug content, an (b)(4) safety system to avoid sharps injury after use and an (b)(4) finger flange to facilitate PFS-S grasping and handling.

Table 2 - Description of the plunger rod

<table>
<thead>
<tr>
<th>Material/Type</th>
<th>Color</th>
<th>Supplier</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
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</table>

Table 4 - Description of the finger flange

<table>
<thead>
<tr>
<th>Material/Type</th>
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<tbody>
<tr>
<td></td>
<td>White</td>
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Table 6 - Description of the safety system components

<table>
<thead>
<tr>
<th>Component part</th>
<th>Material/Type</th>
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<th>Supplier</th>
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<tr>
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<td></td>
<td>Clear</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Metal</td>
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</tr>
</tbody>
</table>
Reviewer comment:
On October 14, 2016, the sponsor clarified the (c)(4) cleared under (b)(4) in not applicable to this application. Sanofi receives a certificate of conformity from the supplier of each component of the safety system. Quality control tests are performed by a subcontractor or by Sanofi. Incoming controls are performed on every batch using sampling per ISO 2859-1. The sponsor has provided drawings, specifications and a list of controls performed on each component.

The sponsor referenced (b)(4) as the appropriate 510(k) for this submission. No additional information is needed.

4. Review:

Design Verification Pre-filled Syringe (PFS) (Report QUA- (b)(4) 2015-20986 Section 3.2.P.2.4)
The following functional performance tests were performed on the glass syringes as a standalone product. Tests required according to ISO 11040-4: Prefilled Syringes Part 4: Glass Barrel for Injectable were performed for dupilumab bulk prefilled syringe. ISO 11040-4 requirements, an assessment of their applicability to the dupilumab presentations, and a rationale for the assessment are provided in QUA- (b)(4) 2015-20986 Table 16.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specifications</th>
<th>Result</th>
<th>Result status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seal integrity Testing (Dye immersion test - RWS)</td>
<td>Test 1: 32 syringes</td>
<td></td>
<td>No methylene blue observed</td>
<td>Meets</td>
</tr>
<tr>
<td></td>
<td>Test 2: 32 syringes</td>
<td></td>
<td>No methylene blue observed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 3: 32 syringes</td>
<td></td>
<td>No methylene blue observed</td>
<td></td>
</tr>
<tr>
<td>Break Force and Gliding Force (with water)</td>
<td>Test 1: 32 syringes</td>
<td></td>
<td>Break Force (N): Min: 3.52, Max: 5.40; SD: 0.43</td>
<td>Complies</td>
</tr>
<tr>
<td></td>
<td>Test 2: 32 syringes</td>
<td></td>
<td>Glide Force (N): Min: 2.03, Max: 3.57; SD: 0.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 3: 32 syringes</td>
<td></td>
<td>Break Force (N): Min: 3.97, Max: 5.66; SD: 0.38</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glide Force (N): Min: 1.68, Max: 3.63; SD: 0.43</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Break Force (N): Min: 3.43, Max: 5.34; SD: 0.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glide Force (N): Min: 2.06, Max: 3.84; SD: 0.44</td>
<td></td>
</tr>
<tr>
<td>Separation force (Needle pull out force)</td>
<td>Test 1: 32 syringes</td>
<td>Min: 99 N, Max: 107 N, SD: 2</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 2: 32 syringes</td>
<td>Min: 91 N, Max: 102 N, SD: 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 3: 32 syringes</td>
<td>Min: 90 N, Max: 112 N, SD: 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stress cracking (Burst test)</td>
<td>50 syringes</td>
<td>The lowest pressure needed to burst the syringe was above 100 bar</td>
<td>There is no specification for this test</td>
<td></td>
</tr>
<tr>
<td>Dead space (Dead Volume)</td>
<td>Test 1: 32 syringes</td>
<td>Min 2 µl, Max 21 µl</td>
<td>Complies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 2: 32 syringes</td>
<td>Min 4 µl, Max 32 µl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 3: 32 syringes</td>
<td>Min 3 µl, Max 21 µl</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 11 - Functional Performance results (Continued)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specifications</th>
<th>Result</th>
<th>Result status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tip cap removal force</td>
<td>Test 1: 32 syringes</td>
<td>(b) (4)</td>
<td>Min: 10 N, Max: 16 N</td>
<td></td>
</tr>
<tr>
<td>(Rigid Needle shield removal force)</td>
<td>Test 2: 32 syringes</td>
<td></td>
<td>Min: 7 N, Max: 15 N</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 3: 32 syringes</td>
<td></td>
<td>Min: 12 N, Max: 18 N</td>
<td></td>
</tr>
<tr>
<td>Piston seal blowback</td>
<td>Test 1: 32 syringes</td>
<td>No leakage observed</td>
<td></td>
<td>Compiles</td>
</tr>
<tr>
<td>(Leak test)</td>
<td>Test 2: 32 syringes</td>
<td>No leakage observed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Rigid Needle shield removal)</td>
<td>Test 3: 32 syringes</td>
<td>No leakage observed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piston seal blowback</td>
<td>Test 1: 32 syringes</td>
<td>No leakage observed</td>
<td></td>
<td>Compiles</td>
</tr>
<tr>
<td>(tightness test)</td>
<td>Test 2: 32 syringes</td>
<td>No leakage observed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 3: 32 syringes</td>
<td>No leakage observed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Needle penetration force</td>
<td>Test 1: 32 syringes</td>
<td>Mean: 0.93N, Max: 0.78N, Min: 0.65N</td>
<td></td>
<td>There are no specifications for this test</td>
</tr>
<tr>
<td></td>
<td>Test 2: 32 syringes</td>
<td>Mean: 0.78N, Max: 1.0N, Min: 0.65N</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 3: 32 syringes</td>
<td>Mean: 1.00N, Max: 0.82N, Min: 0.65N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass Flange breakage resistance</td>
<td>Test 1: 32 syringes</td>
<td>Mean: 357N, Max: 716N, Min: 121N</td>
<td></td>
<td>Compiles</td>
</tr>
<tr>
<td></td>
<td>Test 2: 32 syringes</td>
<td>Mean: 339N, Max: 831N, Min: 163N</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test 3: 32 syringes</td>
<td>Mean: 347N, Max: 862N, Min: 193N</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5D: Standard deviation

Reviewer Comment:
Tests performed on the prefilled syringe (PFS) are deemed acceptable and were performed to ISO 11040-4. The sponsor has provided rationale for tests not performed to the ISO 11040-4 requirements, as they were not applicable to the device constituent parts. This is Adequate.

Container Closure Integrity Testing:
CCI Test by dye ingress is conducted in conjunction with sterility testing on PFS-S stored at the long-term storage condition of 2 to 8 °C (Module 3.2.P.8.2.). Furthermore, CCI Test by dye ingress is tested annually as part of long-term primary (on Bulk PFS) and supporting (on PFS-S) stability studies (Module 3.2.P.8.1.).

Prefilled Syringe with Safety Feature-(PFS-S) Design Verification (Report QU<sup>2</sup> 2015-21398):
Dimensional compatibility of plunger rod with the plunger stopper:
Regarding the compatibility of the plunger rod with the plunger stopper, a pre-evaluation of the connectivity between these two device constituent parts was done prior to the performance by a test consisting of screwing entirely the plunger rod into the plunger stopper (by limiting at the maximum the plunger stopper movement and rotation) and by checking the effectiveness of the connection between the two components (i.e., no gap between the top of the plunger stopper and the bottom of the plunger rod) on a sample of 32 syringes. The test demonstrated the effectiveness of the connectivity on each sample.

The key PFS-S performance tests were identified as part of the “Essential Design Outputs” (EDO) to ensure the usability of the PFS-S which is considered as the combination product.

Five tests performed on measuring equipment, allow physical evaluation of the combination product close to its intended use by the final users:
• Break loose and glide forces
• RNS removal force (RNS pull out force)
• Delivery volume
• Safety system activation
• Safety system unlocking force after activation

These key PFS-S performance tests will be monitored during on-going stability studies (3.2.P.8 Stability).

Length of time or speed at which the user should deliver the dose with the PFS-S: Not controlled as a length of time or a speed but assessed through the glide force specification which establishes the mean force required to deliver the drug and ensure that the PFS-S is sufficiently easy for the users to use. Indeed, the speed of injection is chosen by the user based on a number of factors, such as comfort at a given injection site of the patient receiving the injection and the comfort in the hand of the user delivering the injection. For this reason, the time taken by users to complete an injection with the PFS-S varies considerably and is not determined.

Additionally to the key performance tests, a free fall test was performed in the frame of the design control based on ISO 11608-1 Needle-based injection systems for medical use.

During the design verification stage, the applicable performance tests of the PFS-S were performed on 3 batches filled and assembled using the validated process.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specification</th>
<th>Batch</th>
<th>Results</th>
<th>Test status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>RNS removal force (RNS pull out force)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simple sampling plan with control level</td>
<td>As per acceptance limit defined in internal procedure</td>
<td>5L091A</td>
<td>8.616</td>
<td>5.811</td>
</tr>
<tr>
<td></td>
<td>I according to ISO9869-1</td>
<td></td>
<td>5L096A</td>
<td>8.007</td>
<td>5.160</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L092C</td>
<td>9.585</td>
<td>6.751</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specification</th>
<th>Batch</th>
<th>Results</th>
<th>Test status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Break loose force</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Simple sampling plan with control level</td>
<td>As per acceptance limit defined in internal procedure</td>
<td>5L091A</td>
<td>7.542</td>
<td>1.021</td>
</tr>
<tr>
<td></td>
<td>II according to ISO3881-1</td>
<td></td>
<td>5L096A</td>
<td>7.610</td>
<td>0.829</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L092C</td>
<td>7.772</td>
<td>1.029</td>
</tr>
</tbody>
</table>
### Table 13 - PFS-S Gliding force test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specification</th>
<th>Batch</th>
<th>Mean (N)</th>
<th>SD (N)</th>
<th>Mean ± k*SD (N)</th>
<th>Test status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glide force test</td>
<td>Simple sampling plan with control level I according to ISO2859-1</td>
<td>As per acceptance limit defined in internal procedure</td>
<td>5L091A</td>
<td>10.389</td>
<td>0.737</td>
<td>11.896</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L090A</td>
<td>10.201</td>
<td>0.891</td>
<td>11.604</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L092C</td>
<td>10.226</td>
<td>0.638</td>
<td>11.522</td>
<td>Compliant</td>
</tr>
</tbody>
</table>

### Table 14 - PFS-S Delivery volume test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specification</th>
<th>Batch</th>
<th>Mean (ml.)</th>
<th>Min (ml.)</th>
<th>Max (ml.)</th>
<th>Test status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery volume</td>
<td>Simple sampling plan with control level I according to ISO2859-1</td>
<td>As per acceptance limit defined in internal procedure</td>
<td>5L091A</td>
<td>2.1276</td>
<td>2.1089</td>
<td>2.139</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L090A</td>
<td>2.1215</td>
<td>2.1105</td>
<td>2.1352</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L092C</td>
<td>2.1268</td>
<td>2.1082</td>
<td>2.1615</td>
<td>Compliant</td>
</tr>
</tbody>
</table>

### Table 15 - Safety system activation and locking test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specification</th>
<th>Batch</th>
<th>Results</th>
<th>Test status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety system activation</td>
<td>Simple sampling plan with control level I according to ISO2859-1</td>
<td>As per acceptance limit defined in internal procedure</td>
<td>5L091A</td>
<td>Safety system activated and locked</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L090A</td>
<td>Safety system activated and locked</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L092C</td>
<td>Safety system activated and locked</td>
<td>Compliant</td>
</tr>
</tbody>
</table>

### Table 16 - Safety system unlocking force after activation test results

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specification</th>
<th>Batch</th>
<th>Mean (N)</th>
<th>Min (N)</th>
<th>Max (N)</th>
<th>Test status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety system unlocking force after activation</td>
<td>Simple sampling plan with control level I according to ISO2859-1</td>
<td>As per acceptance limit defined in internal procedure</td>
<td>5L091A</td>
<td>98</td>
<td>92</td>
<td>105</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L090A</td>
<td>97</td>
<td>92</td>
<td>105</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L092C</td>
<td>100</td>
<td>92</td>
<td>109</td>
<td>Compliant</td>
</tr>
</tbody>
</table>
3.4.2 Free fall test results

3.4.2.1 Delivery volume results

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specification</th>
<th>Batch</th>
<th>Results</th>
<th>Test status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery volume</td>
<td>30 syringes per batch (10x3 orientations)</td>
<td></td>
<td>5L091A</td>
<td>2.1273, 2.1148, 2.1368</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L090A</td>
<td>2.1316, 2.1146, 2.1575</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L092C</td>
<td>2.1255, 2.1143, 2.1339</td>
<td>Compliant</td>
</tr>
</tbody>
</table>

3.4.2.2 CCI

<table>
<thead>
<tr>
<th>Test</th>
<th>Sampling</th>
<th>Specification</th>
<th>Batch</th>
<th>Results</th>
<th>Test status</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCI</td>
<td>30 syringes per batch (10x3 orientations)</td>
<td>No dye detected</td>
<td>5L091A</td>
<td>No dye detected</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L090A</td>
<td>No dye detected</td>
<td>Compliant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5L092C</td>
<td>No dye detected</td>
<td>Compliant</td>
</tr>
</tbody>
</table>

Reviewer Comment:
The sponsor has completed testing as necessary on the prefilled syringe with safety system. Testing was performed on 3 batches. All batches met the acceptance criteria of each test performed.

IR to Sponsor on 10/25/2016:
You have provided device verification testing on the prefilled syringe with safety feature. It is unclear within Report QUA-7354-2015-21398, the batch sizes that testing was performed on as summarized in Table 10. Please provide the batch sizes and the rationale for the batch sizes used.

Sponsor Response on 10/31/2016:
As requested, the batch sizes sampled for PFS-S Design Verification (DV) Key Performance testing are provided in Table 1.

Table 1: PFS-S Design Verification batch traceability

<table>
<thead>
<tr>
<th>PFS-S Le Trait batch number</th>
<th>Batch size (units of PFS-S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5L090A</td>
<td></td>
</tr>
<tr>
<td>5L091A</td>
<td>(8) (4)</td>
</tr>
<tr>
<td>5L092C</td>
<td></td>
</tr>
</tbody>
</table>
The batch size determination was driven by the needed quantities to support the Design Verification tests. These samples were produced utilizing qualified processes and under GMP conditions ensuring that the quality, safety and performance requirements were met. To have more confidence in the DV results, samples were selected from 3 different batches to introduce potential variations that could result from different runs and components combinations. In addition, the test sample size was determined based on the typical larger commercial batch size resulting in testing more samples for variable testing during the DV testing. The number of units sampled from each batch for DV Key Performance testing is provided in Table 2 below. The sample size for each test was calculated based on the appropriate ISO sampling procedures (ISO 2859-1:1999 for attribute and ISO 3951-1:2013 for variable testing).

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample Size Rationale</th>
<th>Sample Size / batch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Break loose force</td>
<td>ISO 2859-1:2013 Level I</td>
<td>186</td>
</tr>
<tr>
<td>Glide force level</td>
<td>ISO 2859-1:2013 Level II</td>
<td>186</td>
</tr>
<tr>
<td>RNS removal force</td>
<td>ISO 2859-1:1999 Level S3</td>
<td>125</td>
</tr>
<tr>
<td>Delivery volume</td>
<td>ISO 2859-1:1999 Level S3</td>
<td>125</td>
</tr>
<tr>
<td>Safety system activation</td>
<td>ISO 2859-1:1999 Level S3</td>
<td>125</td>
</tr>
<tr>
<td>Safety system unlocking after activation</td>
<td>ISO 2859-1:1999 Level S3</td>
<td>125</td>
</tr>
</tbody>
</table>

Reviewer Comments
The sample sizes for performance testing was provided by the sponsor and the sample sizes are considered ADEQUATE. No additional information is needed.

DESIGN VALIDATION
As part of the Design Control process, systematic risk analyses are conducted to inform and optimize the design of the device and instructions for use (IFU). The results of formative human factors evaluations are analyzed to iteratively refine the final product design and instructions for use in order to render a final product which can be safely and effectively used by the target user groups without patterns of preventable use error. This final product (and IFU) is ultimately tested under simulated use conditions in a summative study to demonstrate the risk control measures (e.g., modifications to the design of the device or the labeling/instructions for use (IFU) implemented adequately address risks, and that any outstanding residual risk is outweighed by the benefits of the product).

Three human factors studies were conducted: two formative evaluations and the summative
human factors validation study, for the dupilumab PFS-S. The purpose of the studies was to demonstrate that any critical risks associated with use of the PFS-S have been identified, assessed and successfully mitigated. The purpose of the summative human factors validation study was to generate evidence that the devices can be used by representative users (under simulated-use conditions) without resulting in use errors that could potentially harm the patients or the users. The study results also provide evidence of the effectiveness of all implemented use-related risk control measures.

The three human factors studies are presented in Module 5 – Human factor Study.

**Reviewer Comment:**
Review of the Human Factors Studies is deferred to CDER DMEPA

**HISTORY OF CHANGES TO PFS-S OVER THE COURSE OF DEVELOPMENT**

During the pharmaceutical development of dupilumab, solution for injection in prefilled syringe assembled in PFS-S.

<table>
<thead>
<tr>
<th>Table 18 - History of changes implemented on the bulk prefilled syringe</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Table 19 - History of changes implemented to the PFS-S.</th>
</tr>
</thead>
</table>
A comparison of the components constitutive of the PFS used in clinical trials with the commercial PFS-S is provided in Table 20.

### Table 20 - Comparison of Clinical PFS Container Closure and commercial PFS-S Container Closure

<table>
<thead>
<tr>
<th>Components</th>
<th>Clinical PFS-SNS</th>
<th>Commercial PFS-S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syringe barrel and needle</td>
<td></td>
<td>(b)(4)</td>
</tr>
<tr>
<td>Needle shield</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plunger stopper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plunger rod</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flange</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety system</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reviewer Comment:**
Changes were made to the PFS by introduction of the RNS as an alternate closure. This change has no impact on the functionality of the device constituent. The sponsor provided a comparison between the _[b](4)_ and RNS in Section 6.1 Report QUA_[b](4) 2015-20986.

The sponsor has provided a comparison of changes of the clinical PFS and commercial PFS-S. Changes have been made in the _[b](4)_ of the device. The sponsor has provided biocompatibility testing on the commercial PFS-S.

**Biocompatibility Testing:**

The sponsor has provided biocompatibility testing for the following components:

- Plunger Rod
- Needle Guard
- Finger Flange

**Reviewer Comments:**
The sponsor has provided Cytotoxicity, Sensitization, Irritation testing on each component within the DMF _[b](4)_. This information was reviewed with the assistance of Sarah Mollo Ph.D (GHDB) The information within the DMF was considered ADEQUATE.

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page.
Reviewer Comments:
The sponsor has provided the information requested and adequately addressed the clarifications biocompatibility concerns of the needle safety guard. There are no deficiencies. The response is adequate.

Release Testing: (Section 3.2.P.5.1)
The release specification for the 150 mg/mL dupilumab solution for injection in prefilled syringe with safety system (PFS-S) contains a complete list of release tests and acceptance criteria covering product solution properties, identity, strength, purity, potency and syringe with safety system performance properties. Several PFS-S release tests are performed on the bulk PFS intermediate. Results obtained from testing the bulk PFS are used to release the final drug product presentation. Release testing performed on the final PFS-S includes appearance of the PFS-S, identity, and functional performance testing.

The specification for dupilumab PFS-S is provided in Table 1 below. Justification of the acceptance criteria is provided in Module P.5.6 Bulk PFS and Module P.5.6 PFS-S.
### Table 1: Specification for Dupilumab Prefilled Syringe with Safety System

<table>
<thead>
<tr>
<th>Test</th>
<th>Analytical Method</th>
<th>Dupilumab PFS-S Acceptance Criteria</th>
<th>End of Shelf Life (Testing Performed on PFS-S)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Release testing performed on Bulk PFS</td>
<td></td>
</tr>
<tr>
<td>Appearance of prefilled with safety system</td>
<td>Visual inspection</td>
<td>Testing not applicable a. No visual defect b. Correct color of plunger rod and finger flange</td>
<td>Not tested</td>
</tr>
<tr>
<td>Expellable Volume</td>
<td>Weighing of expelled liquid USP &lt;1&gt;</td>
<td>2.0 mL minimum expellable volume Result from bulk PFS reported</td>
<td>Same as for release</td>
</tr>
<tr>
<td>Break Loose (BL) and Glide Force (GF)</td>
<td>Force measurement</td>
<td>Result from bulk PFS reported</td>
<td>BL: N GF: N</td>
</tr>
<tr>
<td>Container Closure Integrity</td>
<td>Dye ingress USP &lt;381&gt; Ph. Eur. 3.2.9</td>
<td>Testing not required</td>
<td>No dye detected</td>
</tr>
<tr>
<td>Activation of Safety System</td>
<td>Visual inspection</td>
<td>Testing not applicable</td>
<td>Tested Safety system activated and locked</td>
</tr>
<tr>
<td>Unlocking Force of Safety System</td>
<td>Force measurement</td>
<td>Testing not applicable</td>
<td>Not tested</td>
</tr>
<tr>
<td>Needle Shield Removal Force</td>
<td>Force measurement</td>
<td>Not tested</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

a The applicable SOP defines how conformance to standard is assessed.
b Example electropherogram provided in SOP.

---

**Table 1:** Dupilumab Prefilled Syringe with Safety System Release and Stability Tests Justification

Reference ID: 4049659
3.1.13. **Expellable Volume**

The expellable volume test is performed on the bulk PFS for release and on the finished PFS-S during stability according to the post-approval stability protocol outlined in Module P.8.2 to ensure the expellable volume of the prefilled syringe is consistent with the labeled dosage. The specification is set at 2.0 mL minimum expellable volume based on the volume required to achieve a dose of 300 mg with 150 mg/mL dupilumab. The expellable volume is not expected to change during the PFS-S assembly and final packaging process. Testing during stability studies on the final PFS-S confirms no impact from the assembly and final packaging process on expellable volume.

3.1.14. **Break loose and Glide Forces**

Break loose (BL) and glide force (GF) are tested on the bulk PFS for release and on the finished PFS-S during stability according to the post-approval stability protocol outlined in Module P.8.2. The BL force is the force required to overcome the static friction and initiate movement of the plunger; and the GF is the force needed to maintain axial movement of the plunger down the glass barrel to enable delivery of the drug. The specification for BL and mean GF for the dupilumab PFS have been set at USL $[\text{N}]$ with $k = \hat{\text{N}}$, $n = 186$. The end-of-shelf-life acceptance criteria for BL and GF have been set at USL $[\text{N}]$. Justification of the acceptance criteria is provided in Module P.5.6 Bulk PFS.

3.2.1. **Appearance of Prefilled Syringe with Safety System**

Appearance of the PFS-S is assessed by visual inspection at release to confirm the proper assembly of the PFS-S and freedom from visual defects. The acceptance criteria are as follows:

- No visual defect
- Correct color of plunger rod and finger flange

3.2.3. **Container Closure Integrity**

Container closure integrity testing is not performed at batch lot release but is performed as part of the stability program for PFS-S. The testing is performed using a dye ingress method and the result is expressed as either “pass” or “fail.” The acceptance criterion is set as “no dye detected.”

3.2.4. **Needle Shield Removal Force**
The needle shield removal force test measures the interactions between the needle, the glass barrel and the shield and therefore is independent from the concentration of the drug product. The specification is based on the supplier specification which guarantees the removal force values are between (0)(4) N. Needle shield removal force testing is performed as part of the stability program to confirm that the needle shield removal force remains within the supplier’s specification limits throughout the shelf life of the product.

Therefore, needle shield removal force testing is not performed at batch release.

Functional performance testing was completed during the design verification (Module P.2.4 Container Closure System) and human factors studies were performed with end users to ensure that the needle shield could be successfully removed prior to use (Module 5.3.5.4).

### 3.2.5. Activation of Safety System

Activation of the safety system is not performed at batch lot release, but is performed as part of the stability program. The acceptance criterion is set as “safety system activated and locked” and the result is expressed as either “pass” or “fail.”

### 3.2.6. Unlocking Force of Safety System

Unlocking force of the safety system measures the minimum force needed to unlock the safety system of the PFS-S. The aim of the test is to ensure the locking of the needle safety system after activation to guarantee the efficacy of the needle stick prevention feature. The specification is based on the supplier specification which guarantees the safety system unlocking force (0)(4) N. Unlocking force testing is performed as part of the stability program to confirm that the safety system unlocking force remains within the supplier’s specification limits throughout the shelf life of the product.

Unlocking force of safety system testing is not performed at batch release.

Functional performance testing was completed during the design verification stage to measure the force required to unlock after injection (Module P.2.4 Container Closure System) and human factors studies were performed with end users to ensure efficacy of the needle stick prevention feature (Module 5.3.5.4).

---

**Reviewer Comment:**

Release tests and acceptance criteria has been provided for PFS-S and PFS. The final specifications are provided along with when release testing will be performed. Justifications have been provided for testing on PFS, PFS-S, and end of shelf life testing on PFS-S. The justifications appear to be acceptable. It should be clarified the number of assemblies that will be tested from each lot for each test.

**IR to sponsor on October 25, 2016:**

You have provided release testing and acceptance criteria for the PFS-S and PFS. The final specifications have been provided; however, you have not provided the number of assemblies that will be tested from each lot for each test during release testing. Please clarify the number of assemblies that will be tested during release testing.

---

Reference ID: 4049659
Sponsor Response on 10/31/2016:

The number of units testing is provided in Table 3 of the October 31, 2016 response. The sponsor has provided a table in the response which includes the sample size that will be tested during release testing. The break loose and glide force sample size is 186 samples. The activation of Safety System release testing is currently under development as stated in the October 14, 2016 response to the Agency.

Reviewer Comment:
The sponsor stated in the October 14, 2016 response that the activation of the safety system release testing is currently under development. The sponsor was asked in an IR on January 3, 2017:

You stated in your October 14, 2016 response to the Agency that safety system activation testing development is in progress and planned for implementation. Please provide an update on the development of the safety system testing to be included in the lot release testing.

Sponsor response on January 23, 2017: In the October 14, 2016 response to the agency, the sponsor committed to add activation of the safety system to the release test panel of the finished drug product. The method developed is a manual method and the sampling will be performed according to ISO 2859-1. The development activities are complete and the following BLA sections are updated accordingly:

P.5.1 Specifications PFS-S
P.5.2 Analytical Procedures - PFS-S
P.5.3 Validation of Analytical Procedures - PFS-S
P.5.3 Validation of Manual activation of the Safety System QUA-2017-02259
P.5.6 Justification of Specifications - PFS-S

The sponsor would like to note that during the process of updating Module P.5.2 Analytical Procedures – PFS-S with the manual activation of the safety system test, it was discovered that Table 1 and Section 2.4 incorrectly stated that the activation and unlocking force test was performed at release and on stability. The activation and unlocking force test is only performed on stability, and the new manual activation of the safety system test is performed at release. This has been corrected.

Reviewer comment:
The sponsor has provided an updated test protocol regarding the release testing of the safety system. An updated table of testing performed on the PFS-S has been provided and includes section of the activation of the safety system as part of the lot release testing. The response is ADEQUATE.

Stability Testing:
Table 5 - List of device stability requirements and location

<table>
<thead>
<tr>
<th>Device constituent parts</th>
<th>Device requirements (attributes)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination product (PFS filled with drug assembled with safety system)</td>
<td>Stability after transportation: Visual and dimensional</td>
<td>In Module 3.2.P.3.5 Process validation simulated shipping [QUA 2015-22452]</td>
</tr>
<tr>
<td></td>
<td>Stability after transportation: Functional (break loose and glide force, RNS removal force, delivery volume, safety system activation, safety system unlocking force after activation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stability after transportation: Integrity and asepsis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stability over shelf-life: functional (break loose and glide force, RNS removal force, delivery volume, safety system activation, safety system unlocking force after activation)</td>
<td>In Module 3.2.P.8.1 and 3.2.P.8.3 Stability</td>
</tr>
<tr>
<td></td>
<td>Stability over shelf-life: preservation of drug product quality and efficiency</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 - List of device risk management requirements and location

<table>
<thead>
<tr>
<th>Device constituent parts</th>
<th>Device requirements (attributes)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination product (PFS filled with drug or viscosity mimic solution, assembled with safety system)</td>
<td>The risk analysis must demonstrate that the use, the design and the assembly of the product does not represent any unacceptable risk or use error.</td>
<td>Section 3.3.1.6 and Module 5 - Human factor Study</td>
</tr>
</tbody>
</table>

PFS-S Stability Data (Section 3.2.P.8.1)

The PFS-S studies are being conducted to support and confirm conclusions drawn from the bulk PFS primary stability studies by assessing the impact of the additional time out of refrigeration TOR and handling associated with the PFS-S finishing operations (i.e. addition of plunger rod, finger flange, safety system, labeling, and secondary packaging), and to evaluate stability of the final assembled PFS-S. Data are provided from testing of three stability batches of dupilumab PFS-S (150 mg/mL). These batches were manufactured during PFS-S assembly process validation, and are representative of the commercial process and container closure system.

Shelf life recommendation:

Based on acceptable stability results over a period up to 24 months at the recommended storage condition of 5 ± 3°C (Module P.8.1 Bulk PFS) and comparable stability of the PFS-S to the bulk PFS, the following shelf life and storage conditions are recommended for the PFS-S:

- Preliminary shelf life: 24 months
- Storage temperature: 5 ± 3°C
The stability studies for the three PFS-S primary batches will continue through the 36 month time point as outlined in Table 3. Upon completion of the long-term stability studies, shelf life for dupilumab PFS-S stored at the recommended storage conditions may be extended to 36 months, based on acceptable data. Shelf life extensions based on acceptable data will be communicated in the Annual Report.

**Table 1: Summary of Studies Performed to Assess Dupilumab DP Stability**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-Term Stability</td>
<td>To evaluate the extent of changes to DP quality during long-term storage at the recommended storage conditions, and to establish the dupilumab DP shelf life.</td>
</tr>
<tr>
<td>Accelerated Stability</td>
<td>To support DP manufacturing and handling at ambient temperature for limited time periods, provide support for temperature excursion investigations, and to help identify the likely degradation pathways of dupilumab.</td>
</tr>
<tr>
<td>Stress Stability</td>
<td>To examine the effects of elevated temperatures on dupilumab quality, to identify possible degradation products and degradation pathways of the protein.</td>
</tr>
<tr>
<td>Photostability</td>
<td>To examine the effects of light exposure on drug product</td>
</tr>
</tbody>
</table>

**LONG TERM STABILITY STUDIES**

Stability data are available through six months for three lots of 150 mg/mL dupilumab in PFS-S after storage at the long-term condition. Minimal dupilumab degradation was observed in any of the batches during storage at the long-term condition, and dupilumab continued to meet the acceptance criteria for the monitored attributes after storage at 5°C ± 3°C for six months.

- No meaningful change was observed in tests related to performance (break loose and glide force, volume in container), although an increase in break loose force from approximately 4 N to 6-7 N was observed between t=0 and the initial time point for the assembled PFS-S. All results were well below the specification of 8.4 N, which is set based on the capability of the intended DP user population. Needle shield removal force, activation of safety system, and unlocking force for the safety system was added to the stability protocols after study initiation and will be tested starting from the nine month time point.

- No changes indicating loss of container closure integrity (sterility, dye ingress, or endotoxin) were observed in any stability lots during storage at the long-term condition.

**ACCELERATED STABILITY STUDIES**

Accelerated stability data are available through the three month time point for three lots of 150 mg/mL dupilumab in PFS-S. Minimal dupilumab degradation was observed in any of the batches after one month of storage at the accelerated condition, and all acceptance criteria were met after three months of storage.

No meaningful change was observed in tests related to performance (break loose and glide force, volume in container), although an increase in break loose force from approximately 4 N to 6-7 N was observed.
between t=0 and the 0.5 month accelerated time point for the assembled PFS-S. All results were well below the specification of N, which is set based on the capability of the intended DP user population.

**STRESS STABILITY STUDIES**

Stressed stability data are available through the 3-month time point for one PFS-S lot. The results are summarized below:

No meaningful change was observed in tests related to performance (break loose and glide force, volume in container), although an increase in break loose force from 4 N to 6 N and an increase in glide force from 9 N to 11 N was observed between t=0 and the 1 month accelerated time point for the assembled PFS-S. All results were well below the specification of N, which is set based on the capability of the intended DP user population.

**Reviewer Comments:**

Sponsor has completed long term stability studies on the bulk prefilled syringe, final prefilled syringe and prefilled syringe with safety systems. The device constituent endpoints are identical for all tests performed. There is increase in break loose and glide force, however the specifications were within the acceptance criteria.

**IR to Sponsor on 10/25/2016:**
You have provided long term and accelerated studies for the bulk prefilled syringe, prefilled syringe and prefilled syringe with safety system. Please update your data tables to include the most recent results for all tests performed.

**Sponsor Response 10/31/2016:**

A summary of all bulk PFS lots included in Module P.8.3 Stability Data_Bulk PFS, is provided in Table 4. A brief summary of the updated results is provided following Table 4.

A summary of all PFS-S lots included in Module P.8.3 Stability Data_PFS-S is provided in Table 5, with a brief summary of the updated results provided following the corresponding tables.

Finally, a summary of all PFS lots included in Module P.8.3 Stability Data_PFS is provided in Table 6, with a brief summary of the updated results provided following the corresponding table. Gray shading in the “Available Data (months)” column indicates that additional data is available compared to the initial submission.

**Reviewer Comment to IR:**

The sponsor has provided long term and accelerated stability data for the PFS and PFS-S. It will be requested to update the stability data with most recent data for review. The sponsor has provided accelerated aging data for 3 months accelerated and long term stability data is still ongoing. The sponsor will be asked to update the accelerated aging to support the proposed shelf life of combination product and ensure the device performs as intended at the end of life.

January 23, 2017:

The sponsor updated the accelerated aging to support the proposed shelf life of the combination product. No additional information is required regarding the shelf life claims.
POST-APPROVAL STABILITY PROTOCOL AND STABILITY COMMITMENT (3.2.P.8.2)

The Sponsor commits to complete the stability studies of the primary and supporting dupilumab bulk prefilled syringe (PFS) and prefilled syringe (PFS) batches at the long-term storage condition of 5 °C ± 3 °C according to the stability protocol provided in Module P.8.1_Bulk PFS and Module P.8.1_PFS, respectively.

The Sponsor commits to place a minimum of one batch of dupilumab PFS on long-term stability at the recommended storage condition of 5 °C ± 3 °C every year that manufacturing occurs.

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Interval (months)</th>
<th>0</th>
<th>Initial</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particulate Matter Content</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. particles/container ≤ 10 μm</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>b. particles/container &gt; 10 μm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expellable Volume</td>
<td></td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Break Loose and Glide Force</td>
<td></td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Container Closure Integrity</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Needle Shield Removal Force</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

a “Initial” time point designated as the initiation of the stability study, and will be indicated as the real age of bulk PFS.
LMW = low molecular weight, HMW = high molecular weight; UPLC = ultra performance liquid chromatography
X = required test; NR = not required at this time point; NA = not applicable.

The Sponsor commits to complete the stability studies of the primary and supporting dupilumab bulk prefilled syringe (PFS) and prefilled syringe with safety system (PFS-S) batches at the long-term storage condition of 5 °C ± 3 °C according to the stability protocol provided in Module P.8.1_Bulk PFS and Module P.8.1_PFS-S, respectively.

<table>
<thead>
<tr>
<th>Test</th>
<th>Test Interval (months)</th>
<th>0</th>
<th>Initial</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particulate Matter Content</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. particles</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Expellable Volume</td>
<td></td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Break Loose and Glide Force</td>
<td></td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Container Closure Integrity</td>
<td>NR</td>
<td>X</td>
<td>NR</td>
<td>NR</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Simulated shipping validation studies are performed on packaged dupilumab solution 150 mg/mL in a 2.25 mL prefilled syringes assembled in a safety system (PFS-S). The results of simulated shipping validation according to ASTM D4169 and the protocol of the actual shipping route validation are provided respectively in Module 3.2.P.3.5 Process Validation Simulated Shipping PFS-S [QUA-2015-22452] and in Module 3.2 Actual Shipping Route Qualification [QUA-2016-18581].

Transport stresses, including simulated road (truck), air and sea freight shipping, are evaluated as per ASTM D4169, *Standard Practice for Performance Testing of Shipping Containers and Systems*.

The main objective of shipping validation is to provide documented evidence that product quality and integrity is maintained during transport and handling. The objectives of this simulated shipping validation were to demonstrate the non-impact of road, sea and air freight simulated transport on:

- Visual and dimensional aspects
- Drug product quality
- Performance of the PFS-S syringe (e.g. drug delivery volume, RNS removal force, break loose and glide force, safety system activation and locking)
- Container closure system physical integrity
- Asepsis

Shipping validation is conducted via two validation exercises:

- A simulated shipping validation is performed according to a simulation program defined per ASTM D4169, *Standard Practice for Performance Testing of Shipping Containers and Systems* with the objective to demonstrate the non-impact of transport stress encountered during real shipping by road (truck), air and sea freight on the drug product quality, asepsis, integrity and performance of the PFS-S. The simulation program simulates stresses of the type typically encountered during shipment (e.g. falls, shocks, impacts, and vibrations during the transport, braking, speed control humps, curb, handling with forklift, handling of the maritime or flight container).

Simulated shipping validation is performed on three independent pallets at maximal load and three independent pallets at minimal loads.

Reviewer Comments: The post market stability commitments are acceptable for the device constituents.
## Maximum Load – Performance tests results for dupilumab 150 mg/mL PFS-S

<table>
<thead>
<tr>
<th>Aspect tested</th>
<th>Objectives</th>
<th>Method, sampling plan and acceptance criteria</th>
<th>Result</th>
</tr>
</thead>
</table>
| Break loose force      | Verify that the transport has no impact on the break loose force.          | According to internal validated testing method \(^a\) Single sampling plan with control level II according to ISO 3951-1 Mean \(BL_{\text{Max}} + k \times SD\) \(N\) with \(k = \) \(0.26\) | Pallet A: \(9.146\) N  
Pallet B: \(8.817\) N  
Pallet C: \(9.115\) N |
| Glide force            | Verify that the transport has no impact on the glide force.                | According to internal validated testing method \(^a\) Single sampling plan with control level II according to ISO 3951-1 Mean \(GF_{\text{Mean}} + k \times SD\) \(N\) with \(k = \) \(0.26\) | Pallet A: \(12.117\) N  
Pallet B: \(11.971\) N  
Pallet C: \(11.325\) N |
| Activation and locking of the safety system | Verify that the transport has no impact on the activation and locking of the safety system | According to internal validated testing method \(^a\) Single sampling plan with control level II according to ISO 2859-1 Visual examination (pass/fail): safety system activated and locked after emptying the syringe | Pass  
Pass  
Pass |
| Unlocking force of the safety system | Verify that the transport has no impact on the unlocking force of the safety system | According to internal validated testing method \(^a\) Single sampling plan with control level II according to ISO2859-1 Unlocking force \(N\) | Min: 119 N  
Min: 116 N  
Min: 115 N |
| Delivery volume        | Verify that the transport has no impact on the expellable volume           | According to internal SOP \(^a\) Test performed on 5 syringes per pallet Expellable volume \(\geq\) 2.0 mL | Min: 2.1 mL  
Min: 2.1 mL  
Min: 2.1 mL |
RNS removal force

Verify that the transport has no impact on the RNS removal force

According to internal validated testing method \(^a\)

Single sampling plan with control level S4 according to ISO 2859-1

<table>
<thead>
<tr>
<th>Aspect Tested</th>
<th>Objectives</th>
<th>Method, sampling plan and acceptance criteria</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Break loose force</td>
<td>Verify that the transport has no impact on the break loose force.</td>
<td>Mean (\text{BLMax} + k \times \text{SD} = 9.277) N</td>
<td>Pallet D: Mean (\text{BLMax} + k \times \text{SD} = 8.522) N</td>
</tr>
<tr>
<td>Glide force</td>
<td>Verify that the transport has no impact on the glide force.</td>
<td>Mean (\text{GFMean} + k \times \text{SD} = 12.066) N</td>
<td>Pallet D: Mean (\text{GFMean} + k \times \text{SD} = 12.692) N</td>
</tr>
<tr>
<td>Activation and locking of the safety system</td>
<td>Verify that the transport has no impact on the activation and locking of the safety system</td>
<td>Pass</td>
<td>Pass</td>
</tr>
</tbody>
</table>

\(a\) CCIT by dye ingress method is described in Module 3.2.P.5.2 Analytical Procedure - Container Closure Integrity [QUA 2016-13647].

Minimum Load - Performance tests results for dupilumab 150 mg/mL PFS-S
<table>
<thead>
<tr>
<th>Activity</th>
<th>Verification</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Break loose force</td>
<td>Verify that the transport has no impact on the break loose force.</td>
<td>According to internal validated testing method. Single sampling plan with control level II according to ISO 3951-1</td>
<td>Mean BL Max + k x SD = 9.277 N Mean BL Max + k x SD = 8.522 N Mean BL Max + k x SD = 9.280 N</td>
</tr>
<tr>
<td>Glide force</td>
<td>Verify that the transport has no impact on the glide force.</td>
<td>According to internal validated testing method. Single sampling plan with control level II according to ISO 3951-1</td>
<td>Mean GF Mean + k x SD = 12.066 N Mean GF Mean + k x SD = 12.692 N Mean GF Mean + k x SD = 11.712 N</td>
</tr>
<tr>
<td>Activation and locking of the safety system</td>
<td>Verify that the transport has no impact on the activation and locking of the safety system</td>
<td>According to internal validated testing method. Single sampling plan with control level II according to ISO 2859-1 Visual examination (pass/fail): safety system activated after emptying the syringe</td>
<td>Pass Pass Pass</td>
</tr>
<tr>
<td>CCIT</td>
<td>Verify that the transport has no impact on the container closure integrity</td>
<td>CCIT by dye ingress performed according to internal SOP. Test performed on 32 syringes per pallet No dye detected</td>
<td>No dye detected No dye detected No dye detected</td>
</tr>
</tbody>
</table>

CONCLUSION

The controls performed after the simulation of transport showed that the visual, functional, microbiological tested aspects of PFS-S as well as the product quality including integrity of the PFS-S confirm the absence of transport impact.

Reviewer comment:
The sponsor provided shipping validation testing to confirm transport had no impact on the device constituents.

Risk Analysis:
A risk analysis was performed to identify risks associated with the device constituent part of the combination products: the prefilled syringe presentation (PFS) and the prefilled syringe in safety system presentation (PFS-S). This risk analysis included risks associated with the device design, its packaging and labeling (including the IFU), the intended uses and the manufacturing
process. Evaluation of the identified risks determined which risks required mitigation, and risk control measures were designed for each of them. Those control measures were then implemented, verified and validated.

- Design Verification: The implemented risk control measures were confirmed via design verification tests. The successful results demonstrated that the design specifications were fulfilled and that the design output met the design input requirements.

- Design Validation: The implemented risk control measures were validated via a Human Factors Validation Study for each presentation. The successful results demonstrated that the dupilumab PFS and PFS-S were safe and effective in the hands of the intended users.

A risk / benefit analysis was then conducted on all the use-related and device technical residual risks associated with the PFS and the PFS-S. A summary of the evaluation of all risks associated with the devices, including all residual risks that were in the “yellow” region after risk mitigation (indicating that a risk / benefit analysis was required) are shown in Appendix 1 and Appendix 2, respectively, for PFS-S and PFS. The risk / benefit analyses were reviewed and the residual risks were approved by senior management, in compliance with ISO 14971:2007.

**RISK MANAGEMENT ACTIVITIES SUMMARY RELATED TO DEVICE CONSTITUENT PART: PREFILLED SYRINGE IN SAFETY SYSTEM**

**Implementation of Risk Management Plan**

The risk management strategy and acceptance criteria used for the Dupilumab PFS-S are the following:

- Risk evaluation before risk control measures
- Implementation and verification of the risk control measures
- Risk evaluation of the overall residual risks after risk control measures
  - Green region: Acceptable risk
  - Yellow region: A comprehensive risk / benefit analysis must be performed, reviewed and approved by the sponsor’s senior management
  - Red region: Unacceptable risk

For risks in the green region, all risk control options must be considered to further mitigate the risk. If no further mitigation is feasible, the risk can be accepted, given that the risk is outweighed by the benefits.

If a risk remains in the yellow region and a thorough analysis did not identify any more feasible options for risk control, a comprehensive risk/benefit analysis must be undertaken. The result of this risk/benefit analysis must be reviewed and approved by the sponsor’s senior management, in compliance with ISO 14971:2007.

If a risk remains in the red region it is considered unacceptable.

**Risk Assessment for Use**

In total, 40 hazardous situations were identified. Of those, 6 were rated in the red region (“unacceptable”) and 22 entries were identified within the yellow region (risk/benefit analysis required) before implementation of risk control measures.
With the implemented risk control measures, no risk remains in the red (unacceptable) region. The majority of all risks have been mitigated to the green (acceptable) region.

Some risks (14 in total) remained in the yellow region after all risk control measures were implemented.

**Design FMEA (device technical risks)**

In total, 41 hazardous situations were identified. Of those, 17 were rated in the red region (“unacceptable”) and 11 entries were identified within the yellow region (risk/benefit analysis required) before implementation of risk control measures.

With the implemented risk control measures, no risk remains in the red region (unacceptable). The majority of all risks have been mitigated to the green region (acceptable).

A limited number of risks (18 in total, shown in Table 15) remained in the yellow region after all risk control measures were implemented:

- **S5 severity**: Six (6) risks have an occurrence of “negligible” (10^-8 or less).
- **S4 severity**: Ten (10) risks have an occurrence of “improbable” (10^-7 or less); and two (2) risks have an occurrence of “infrequent” (10^-6 or less).

**Design FMEA (device technical risks)**

In total, 41 hazardous situations were identified. Of those, 17 were rated in the red region (“unacceptable”) and 11 entries were identified within the yellow region (risk/benefit analysis required) before implementation of risk control measures. Figure 2 shows the resulting risk graph before implementation of risk control measures.

![Risk Graph Before Implementation of Risk Control Measures](image)

**Identification, implementation, verification and validation of risk control measures**

For all causes, risk control options were considered to further mitigate the risk to the patient. All the required risk control measures were successfully implemented, verified and validated.
As part of the mitigation plan, a portion of the risk control measures were controlled by design and these measures were confirmed in design verification tests in order to ensure the device output met the design input requirements. The results of the design verification tests demonstrated that all the design specifications related to the drug device combination and its components were fulfilled. The effectiveness of the risk control measures implemented to control the use-related risks was validated in the Human Factors Validation Study [QUA-FD-2016-15779]. These activities were successfully passed and the dupilumab PFS-S was shown to be safe and effective in the hands of the intended users.

With the implemented risk control measures, no risk remains in the red (unacceptable) region. The majority of all risks have been mitigated to the green (acceptable) region.

Some risks (14 in total, shown in Table 14) remained in the yellow region after all risk control measures were implemented:

- S5 severity: Seven (7) risks have an occurrence of “negligible” ($10^{-8}$ or less).
- S4 severity: Five (5) risks have an occurrence of “infrequent” ($10^{-7}$ or less).
- S2 severity: Two (2) risks have an occurrence rate of “remote” ($10^{-5}$ or less).

**Design FMEA (Assessment of device technical risks)**

Figure 4 displays the resulting risk graph after implementation of risk control measures for the device technical risks.

**Figure 4: dFMEA (device technical risks) - Risk graph after implementation of risk control measures**

With the implemented risk control measures, no risk remains in the red (unacceptable) region. The majority of all risks have been mitigated to the green (acceptable) region.

A limited number of risks (18 in total, shown in Table 15) remained in the yellow region after all risk control measures were implemented:

- S5 severity: Six (6) risks have an occurrence of “negligible” ($10^{-8}$ or less).
- S4 severity: Ten (10) risks have an occurrence of “improbable” ($10^{-7}$ or less); and two (2) risks have an occurrence of “infrequent” ($10^{-6}$ or less).
Overall risk/benefit analysis
A risk/benefit analysis was then performed on the overall residual risk associated with the device constituent part of the PFS-S. The individual residual risks and the overall residual risk, considering the benefit of the dupilumab PFS-S treatment, were reviewed and accepted by the sponsor’s senior management, in compliance with ISO 14971:2007.

In total 39 hazardous situations were identified. Of those, 6 were rated in the red region (“unacceptable”) and 22 entries were identified within the yellow region (risk/benefit analysis required) before implementation of risk control measures. Figure 5 shows the resulting risk graph before implementation of risk control measures.

![Figure 5: Use-related risk analysis - Risk graph before implementation of risk control measures](image)

Design FMEA (Assessment of device technical risks)
In total 34 hazardous situations were identified. Of those, 4 were rated in the red region (“unacceptable”) and 18 entries were identified within the yellow region (risk/benefit analysis required) before implementation of risk control measures. Figure 6 shows the resulting risk graph before implementation of risk control measures.
Identification, implementation, verification and validation of risk control measures

For all causes all risk control options were considered to further mitigate the risk to the patient. All the required risk control measures were successfully implemented, verified, and validated.

As part as the mitigation plan, a portion of the risk control measures were controlled by design and these measures were confirmed in design verification tests in order to ensure the device output met the design input requirements. The results of the design verification tests demonstrated that all the design specifications related to the drug device combination and its components were fulfilled. The effectiveness of the risk control measures implemented to control the use-related risks was validated in the Human Factors Validation Study [QUA-FD-2016-16606]. These activities were successfully passed and the dupilumab PFS was shown to be safe and effective in the hands of the intended users.

Risk evaluation after risk control measures

With the implemented risk control measures, no risk remained in the red (unacceptable) region. The majority of all risks have been mitigated to the green (acceptable) region. Some risks (14 in total, shown in Table 16) remained in the yellow region (risk/benefit analysis required) after all risk control measures were implemented:

- S5 severity: Five (5) risks have an occurrence of “negligible” (10^-8 or less) and two (2) risks have an occurrence of “infrequent” (10^-7 or less).
- S4 severity: Five (5) risks have an occurrence of “infrequent” (10^-7 or less).
- S2 severity: Two (2) risks have an occurrence rate of “remote” (10^-5 or less).

Design FMEA (Device technical risk analysis)

Figure 8 displays the resulting risk graph after implementation of risk control measures for the device technical risks.

Figure 8: dFMEA (device technical risks) - Risk graph after implementation of risk control measures
With the implemented risk control measures, no risk remains in the red region (unacceptable). The majority of all risks have been mitigated to the green region (acceptable). A limited number of risks (12 in total, shown in Table 17) remained in the yellow region (risk/benefit analysis required) after all risk control measures were implemented:

- S5 severity: Two (2) risks have an occurrence of “negligible” (10^-8 or less).
- S4 severity: Ten (10) risks have an occurrence of “improbable” (10^-7 or less).

In compliance with the risk management process, the individual residual risks were analyzed.

### Individual risk/benefit analysis

As described above, the treatment of atopic dermatitis with dupilumab is estimated to provide a certain benefit when compared to the standard treatments available.

Most of the residual risks associated with the device constituent part were in the green (acceptable) region after risk control measures were implemented and therefore can be accepted.

Following the risk analysis in Section 1.11, a limited number of risks associated with the device constituent part remained in the yellow region of the risk graph after implementation of control measures requiring a comprehensive analysis of the risk/benefit.

The assessment of use-related risks resulted in 14 residual risks in the yellow region and the assessment of device technical risks resulted in 12 risks in the yellow region. These risks were reduced to the greatest feasible extent. For these risks, considering on the one hand the low probability of occurrence associated with every individual risk and on the other hand the benefit of the dupilumab treatment, the risk/benefit for each individual risk in this region is in favor of the benefit. Therefore the risks are acceptable.

### 1.12.3. Overall risk/benefit analysis

A risk/benefit analysis was then performed on the overall residual risk associated with the device constituent part of the PFS. The individual residual risks and the overall residual risk, considering the benefit of the dupilumab PFS treatment, were reviewed and accepted by the sponsor’s senior management, in compliance with ISO 14971:2007.

### Reviewer Comments:

The risk analysis provided in the submission is considered acceptable. The sponsor conducted a risk analysis and dFMEA reducing all unacceptable risks. The majority of risks had been mitigated to the green region. A risk/benefit analysis was conducted on the risks which remained in the yellow region.
The analysis determined that the risk in this region is in favor of the benefit. The information is Adequate.

| ISO 23908 Sharps Injury Protection | Not performed-referencing performed by device manufacturer |
| ISO 11040-4 -Prefilled Syringes Part 4 | 3.2.P.2.4 Report QUA-15-20986 |
| Human Factors | Module 5 |

5. Comments:

The following information request be sent to the applicant on September 22, 2016 with the sponsor’s response received on October 14, 2016.

In Module 3.2.P.2.4, it is stated a risk management plan is designed prior to a risk assessment, however a risk analysis could not be located for the device constituent.

**Reviewer Comment:**
See review under risk Management. The sponsor provided a risk analysis as a dFMEA and the information provided was adequate. All risks were mitigated to yellow or green region. For risks that were in the yellow region as risk/benefit analysis was conducted. This is ADEQUATE.

In Section 3.2.P.2, [b][4] has provided a biocompatibility Summary of the applicable device components, it is requested that the DMF holder provide the location of the full biocompatibility tests performed which include cytotoxicity, sensitivity and irritation testing.

**Reviewer Comments:**
The MAF holder had provided all requested biocompatibility tests and tests conducted were considered ADEQUATE. See Biocompatibility Section for additional information.

A description of the needle safety feature has been provided however, it is requested the DMF holder provide the location within the DMF file for the specifications to the constituents.

**Reviewer Comment:**
The sponsor updated the information provided to state that the specifications for the needle safety feature are found in [b][4] and the submission has been updated to reflect that information.

The applicant states the Needle Guard is cleared under [b][4], however a letter of authorization could not be located from the 510k holder. Please provide a letter of authorization so that the Agency can review the safety and efficacy data within the associated 510k submission. Without the letter of authorization, we will not be able to leverage any data associated in the associated 510k to support your combination product.

**Reviewer Comment:**
The sponsor updated the information in the submission to reference [b][4] as the appropriately cleared 510(k) for the needle safety feature. The 510(k) references compatible plunger rods to be used with the device. It is unclear based upon the information provided if the proposed plunger rod is on hat is cleared for use with the device. The sponsor will be asked to clarify that and provide testing to support the use of the proposed plunger rod if it is not in the 510(k).
The sponsor provided a response on January 23, 2017 stating that the proposed plunger rod intended to be used was cleared under the and . The needle Guard was cleared with a traditional premarket notification and 2 subsequent modifications via Special 510(K0. The supplier confirmed that the proposed plunger rod for was cleared in the traditional 510(k) and

**Reviewer Comment:**
The sponsor’s response is Adequate. No additional information is needed.

**IR to Sponsor on September 22, 2016:**
In section, 3.2.P.8.3 long-term storage stability data to support shelf life will include testing of needle safety feature at end of shelf life however, accelerated aging stability data does not include testing of the needle safety feature as an endpoint to support the end of shelf life performance. It should be noted that the sponsor has provided a post market commitment to update the real time aging studies and safety feature is part of the lot release testing of the device. The sponsor also has provided the suppliers aging data to support the use of the

**Sponsor Response on October 14, 2016:**
The performance of the needle safety feature is independent of the contents of the pre-filled syringe; hence, the Sponsor’s intent is to supplement (in this response) the existing long-term stability study with the supplier’s accelerated aging data for the Needle Guard, when tested with a standard 2.25 mL glass syringe. The accelerated aging study was carried out to an equivalent of 4 years of real-time aging, and established that the device functions as intended and in accordance with its performance specifications throughout the shelf life of the product. A summary of relevant sections from this study is provided:

Real time aging tests have been performed at for 1, 2, 3, and 4 years duration. Accelerated aging studies were conducted for a duration of 58 hours at , which is equivalent to four years of real time aging. Sample quantities per test were defined in order to provide 95% confidence and 99% reliability.

**Table 13: Design verification aging study test results**

<table>
<thead>
<tr>
<th>Product Requirement/ Design Input</th>
<th>Acceptance Criteria</th>
<th>Aging Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Status – Time Zero</td>
</tr>
<tr>
<td>Triggering test</td>
<td>Correct triggering along with full activation into locked</td>
<td>Pass</td>
</tr>
<tr>
<td>Compressing force</td>
<td>(b) (4) N</td>
<td>Pass</td>
</tr>
</tbody>
</table>

**Conclusion**

The testing data demonstrate that the Needle Guard met
pre-determined acceptance criteria with acceptable results up to 3 years of real time aging and the equivalent of 4 years with accelerated aging. Real time aging studies are ongoing.

Reviewer Comment:
The sponsor provided acceptable testing that the Needle Guard work as expected with real time aging studies for 3 years and accelerated aging for 4 years.

IR to Sponsor on September 22, 2016:
In section 3.2.P.5.6, release testing does not include activation of safety system or safety system unlocking force. Release testing should include testing to verify the safety system performs as intended after the manufacturing process.

Sponsor Response on October 14, 2016:
The Sponsor commits to add activation of the safety system to the release test panel of the finished product to confirm that the safety system performs as intended after the manufacturing process.

The development activities for inclusion of this distinct safety system activation test are in progress and are planned for implementation prior to the production of the first commercial lot of dupilumab PFS-S product.

However, the Sponsor has determined that the force to override the safety feature is a function of the device design, and not the combination product assembly process. Hence the safety system unlocking force has been challenged and confirmed through design verification testing, in which three independent lots of the final assembled combination product (PFS-S) were tested to measure the force required to override the safety feature. All lots met the pre-determined acceptance criteria and results can be found in Module 3.2.P.2.4 Container Closure System - PFS-S - LTR [QUA-2015-21398]).

The needle guard supplier has also conducted comprehensive design verification testing of the safety system to demonstrate that the safety feature activates as intended and the unlocking force meets requirements to safeguard against unintended sharps injury, as identified in their premarket notification.

Additionally, the activation and locking features of the safety system are tested as part of the routine incoming controls performed on every batch of safety systems received from the supplier prior to assembly operations. Incoming controls performed on the safety system are described in Module 3.2.P.7 Container Closure System – PFS-S – LTR [QUA-2015-21158].

Lastly, the activation and lock out feature was also successfully challenged during the PFS-S assembly process validation in order to demonstrate that the manufacturing process has no impact on the performance of the PFS-S safety lockout feature and force. Results can be found in Module 3.2.P.3.5 Process Validation Assembly 150 – PFS-S – LTR – [QUA-2015-22445]. Hence, the sponsor agrees with conducting activation testing on the safety system at release, but deems that additional testing for unlocking force is not warranted.

RECOMMENDATION:
The reviewer recommends approval of the NDA in the context of device constituent parts for the combination product. The sponsor has provide post approval commitment completing the stability studies of the combination product at long term storage conditions which is adequate.
The sponsor has provided within the BLA application data to support the performance requirements of the device constituent of the combination product. The sponsor had adequately addressed deficiencies submitted in reference to the device constituent and all deficiencies have been resolved.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW E WHITE
02/01/2017
CDRH-Device Constituent consult review entered into DARRTS on behalf of Sapana Patel, PharmD
Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review

Date: January 13, 2017  Date Consulted: August 23, 2016

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health Division of Pediatric and Maternal Health (DPMH)

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

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

To: Division of Dermatology and Dental Products (DDDP)

Drug: Dupixent (dupilumab) injection

BLA: 761055

Subject: Pregnancy and Lactation Labeling

Proposed Indication: For the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids.

Applicants: Regeneron Pharmaceuticals Inc. and Sanofi-Aventis U.S. LLC

Materials Reviewed: July 29, 2016 Applicant’s proposed labeling
- March 31, 2016 and July 29, 2016 Applicant’s submission
- August 23, 2016, DDDP’s request to DPMH-MHT for labeling review
REGULATORY HISTORY
The applicant submitted an original 351 (a) biologic license application (BLA) for Dupixent (dupilumab) injection, BLA 761055, in a rolling submission from March 31, 2016 to July 29, 2016. Dupilumab is a new molecular entity and has been granted breakthrough therapy designation, with priority review (8-month clock). The proposed indication is for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids.

The Division of Dermatology and Dental Products (DDDP) consulted the Division of Pediatric and Maternal Health (DPMH) on August 23, 2016, to assist with reviewing the Pregnancy and Lactation subsections of labeling.

This review provides recommended revisions and structuring of existing information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with current PLLR regulatory requirements.

BACKGROUND
Drug Characteristics
Dupilumab is a recombinant human immunoglobulin G subclass 4 (IgG4) monoclonal antibody, produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture, and binds specifically to the alpha sub-unit of the Type I and II interleukin-4 receptors (IL-4Rα). Dupilumab inhibits IL-4 signaling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signaling through the Type II receptor (IL-4Rα/IL-13Rα). IL-4 and IL-13 are key Type 2 cytokines involved in inflammatory response in atopic dermatitis. Dupilumab is expected to inhibit the Type-2 helper T cell (Th2) pathway selectively, which is responsible for several pathophysiological mechanisms. The applicant believes that dupilumab’s downregulation may prevent or reverse the development of atopic dermatitis (AD).

Dupilumab has a molecular weight of 147,000 Daltons. Bioavailability was greater than 90% following SC dosing in monkey and approximately 85% following SC dosing in rat. In humans, the bioavailability of dupilumab following a SC dose is estimated to be 64%. Dupilumab did not promote substantial immunogenicity following dosing in cynomolgus monkeys.1,2

Pregnancy and Lactation Labeling Rule (PLLR)
On June 30, 2015, the “Content and Format of Labeling for Human Prescription Drug and

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1 Pharmacology/Toxicology Review in DARRTS by Renqin Duan, Ph.D., dated December 5, 2016. Reference ID: 4022745
2 Applicant’s submission and proposed labeling, July 29, 2016
Biological Products; Requirements for Pregnancy and Lactation Labeling,”3 also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect. 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 create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule4 format to include information about the risks and benefits of using these products during pregnancy and lactation.

REVIEW
Pregnancy
Nonclinical Experience
Dupilumab may be transmitted from the mother to the developing fetus. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD). The postnatal growth and development of the offspring was monitored for a period of 6 months postpartum. Eighty five percent of offspring had had measurable serum concentrations 28 days post-birth, and those with mothers in the 100 mg/kg/week dose group had measurable concentrations 91 days post-birth. No treatment related effects on clinical signs, body weight, physical examinations, infant measurements, neurobehavioral assessment, organ weight or skeletal evaluations were noted during the postnatal period. The reader is referred to the Pharmacology/Toxicology review by Renqin Duan, Ph.D., for further details.

Review of Literature
DPMH searched PubMed, Embase, ReproTox and TERIS databases for information regarding dupilumab and use during pregnancy. No published information was identified. As per the applicant, no studies of dupilumab have been conducted in pregnant women.

Review of Clinical Trials
Because the drug has not yet been approved, no pharmacovigilance database has been established. In the clinical trials, pregnant or breastfeeding women or women who planned to become pregnant or breastfeed during the study period were excluded from these trials. As of the data cutoff date of April 27, 2016, a review of cases of pregnancy reported revealed a total of 32 pregnancies in patients treated with dupilumab and 17 pregnancies in partners of male patients exposed to dupilumab. The 32 pregnancies in study patients have led to 7 healthy live births (8 healthy infants- including one set of twins), 2 induced (elective) abortions (no fetal malformations were reported as cause for the induced abortion-only personal reasons), and 6 spontaneous abortions, with the remaining 10 pregnancies ongoing and the rest as lost to follow-up. Of the 6 study patients with spontaneous abortion, 2 patients had 1 or more factors known to increase the risk of spontaneous abortion (i.e., elevated parathyroid hormone, clotting disorders, and history of

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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).
4 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).
infertility). The 17 partner pregnancies of male trial patients have led to 5 live births (5 healthy infants), 1 induced (elective) abortion (partner of a male patient treated with placebo during the clinical trial-no information is available), and 2 spontaneous abortions, with 8 pregnancies ongoing and 1 lost to follow-up. These limited clinical data are insufficient to draw meaningful safety conclusions about the effects of dupilumab during pregnancy. No signals have been identified and no major concerns exist up to now.

Table 1: Cumulative birth outcomes for maternal exposure pregnancies to dupilumab in the applicant’s clinical development program* through April 27, 2016

<table>
<thead>
<tr>
<th>Birth Outcomes</th>
<th>Maternal Exposures (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal live birth</td>
<td>8 (1 set of twin)</td>
</tr>
<tr>
<td>Full term birth with complications</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous abortion NOS</td>
<td>6</td>
</tr>
<tr>
<td>Induced (elective) Termination</td>
<td>2</td>
</tr>
<tr>
<td>Ongoing pregnancies</td>
<td>10</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: NOS not otherwise specified.
*All investigational indications including atopic dermatitis, asthma, and nasal polyposis

Summary
Limited available data with dupilumab use in pregnant women are insufficient to inform a drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, dupilumab may be transmitted from the mother to the developing fetus. No expected or theoretical risks exist.

Intended and unintended exposures during pregnancy will likely occur. In addition, safety data regarding exposure during pregnancy are lacking because pregnant women were excluded during dupilumab’s clinical development program, and limited outcome data are available on the women who became pregnant in the clinical trials. Therefore, the applicant proposes a post-approval study (a voluntary pregnancy exposure registry) to assess outcomes following exposure in pregnancy to characterize dupilumab’s safety in pregnancy.

Reviewer’s Comments
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. 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. Combining a pregnancy registry with a

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5 FDA Guidance for Industry Establishing Pregnancy Exposure Registries  
6 FDA webpage Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During
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. The applicant should provide the registry protocol for further review and evaluation.

**Lactation**

**Nonclinical Experience**

There are no nonclinical studies for lactation.

**Review of Literature**

DPMH conducted a search of Medications and Mother’s Milk, the Drugs and Lactation Database (LactMed), Micromedex, and of published literature in PubMed using the search terms “dupilumab and lactation” and “dupilumab and breastfeeding.” No reports of clinical lactation studies or case reports of dupilumab use in lactating women were found in published literature.

**Summary**

There are no data on the presence of dupilumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal human IgG are present in breast milk in small amounts. Dupilumab, if transferred into breastmilk, may be degraded in the gastrointestinal tract of the breastfeeding infant, however, its effects on the breastfed infant remain unknown. Therefore, DPMH recommends that the following risk/benefit statement is included in section 8.2 of labeling:

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Dupixent and any potential adverse effects on the breastfed infant from Dupixent or from the underlying maternal condition.

**Females and Males of Reproductive Potential**

**Nonclinical Experience**

In a fertility study in young sexually mature male and female mice, where dupilumab was administered subcutaneously, no dupilumab related changes in any of the evaluated fertility, early embryonic development and implantation parameters were observed at doses up to 200 mg/kg/week.

**Review of Literature**

DPMH performed a search of published literature on dupilumab and infertility and did not identify any publications.

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Pregnancy in the Post-Approval Setting; Public Meeting http://www.fda.gov/Drugs/NewsEvents/ucm386560.htm

7 Hale, Thomas (2012) Medications and Mothers’ Milk. Amarillo, Texas Hale Publishing
8 http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.
Summary
Animal reproduction studies of administration of dupilumab did not show any adverse effects on fertility. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody. The mutagenic potential of dupilumab has not been evaluated; however monoclonal antibodies are not expected to alter DNA or chromosomes. Therefore, there is no need for pregnancy testing and contraception recommendations. In addition, there are no human data available on the effect of dupilumab on fertility. In conclusion, Section 8.3, Females and Males of Reproductive Potential, will not be included in Dupixent labeling.

CONCLUSION
The Pregnancy and Lactation, sections of Dupixent labeling were structured to be consistent with the PLLR as follows:

- **Pregnancy, Section 8.1**
  - The “Pregnancy” section of Dupixent labeling was formatted in the PLLR format to include: “[4] "Risk Summary," and "Data" sections.

- **Lactation, Section 8.2**
  - The “Lactation” section of Dupixent labeling was formatted in the PLLR format to include the “Risk Summary” section.

RECOMMENDATIONS
1.) DPMH participated in a labeling meeting with DDDP. DPMH revised sections 8.1, 8.2, and 17 of Dupixent labeling for compliance with the PLLR. DPMH refers to the final BLA action for final labeling.
2.) DPMH agrees with the applicant conducting a voluntary pregnancy registry.
APPENDIX A:
DPMH PROPOSED PREGNANCY AND LACTATION LABELING EDITS
FOR DUPIXENT

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
There are no available data on DUPIXENT use in pregnant women to inform any drug associated risk. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. 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
In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary
There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Human IgG is known to be present in human milk. The effects of local gastrointestinal and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother’s
clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOS MASTROYANNIS
01/14/2017

TAMARA N JOHNSON
01/15/2017

LYNNE P YAO
01/19/2017

Reference ID: 4041992
Inter-Center Consultation Memorandum

From: Madan Kumar, DO, CBER/OVRR/DVRPA
To: Brenda Carr, MD, CDER/OND/DDDP
Re: Dupixent (dupilumab, BLA 761055): Proposed labeling of immune responses to non-live vaccines.
Through: Doran Fink, MD, PhD, Team Leader, CBER/OVRR/DVRPA/CRB-2
Andrea Hulse, MD, Branch Chief, CBER/OVRR/DVRPA/CRB-2
Wellington Sun, MD, Director, CBER/OVRR/DVRPA
Date: 12 September 2016

Background/Consultation from CDER/OND/DDDP:

Regeneron Pharmaceuticals has submitted a Biologics License Application (BLA) for Dupixent (dupilumab), a human IL-4 and IL-13 antagonist indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical therapies. In detail, dupilumab is a recombinant human IgG4 monoclonal antibody that binds to the IL-4 receptor alpha sub-unit shared by the IL-4 and IL-13 receptor complexes. The proposed usage is 600mg injected subcutaneously (two 300mg injections in different sites) followed by 300mg given subcutaneously every two weeks.

Both IL-4 and IL-13 are closely related cytokines involved in immune regulation. Although recent evidence has contributed to an understanding that both cytokines play multifunctional roles (including regulation of apoptosis and macrophage activation), a well-established body of literature has traditionally described their role in the differentiation of Th2 cells. IL-4 has classically been regarded as the positive feedback cytokine for Th2 differentiation as well as the major mediator for IgE class switching in B cells. IL-13 is an effector cytokine largely believed to help induce airway hypersensitivity. Together these two cytokines are key mediators of the allergic and T-cell mediated humoral response and have been broadly associated with asthma and atopy.

The proposed package insert states

Also included in the BLA submission are data from a randomized, double-blind, placebo-controlled, parallel group study (R668-AD-1314) to assess the immunization responses to adsorbed tetanus toxoid and meningococcal polysaccharide vaccines. The sponsor proposes the following language with respect to this study:

Immune responses to vaccination were assessed in a study in which patients with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. After 12 weeks of dupilumab administration, patients were vaccinated with a Tdap vaccine Adacel® and a meningococcal polysaccharide vaccine Menomune® responses were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated
The reviewing division (CDER/OND/DDDP) has consulted CBER/OVRR/DVRPA to advise if the applicant’s referenced information supports the above proposed language or to recommend any appropriate changes.

**Discussion of Study R668-AD-1314:**

This was a randomized, double-blind, placebo-controlled, parallel group study to assess the effect of dupilumab on antibody responses to meningococcal (T-cell independent) and tetanus toxoid adsorbed vaccinations (T-cell dependent). The study was conducted over 32 weeks with 194 adult male and female subjects with moderate-to-severe atopic dermatitis. Eligibility criteria excluded subjects who received tetanus or meningococcal vaccine in the past five years, subjects with history of severe allergic reactions to either vaccine, subjects receiving greater than 10mg of daily prednisone or an unstable daily dose of prednisone prior to screening, immunocompromised patients (including HIV infected subjects and subjects on active rituximab therapy). The majority of subjects (64.3%) were white with a mean age of 40 years. Subjects were randomized 1:1 to receive placebo or 300 mg of dupilumab weekly for sixteen weeks. During their week 12 visit subjects were also vaccinated with Adacel (Tdap) and Menomune (meningococcal polysaccharide). Subjects then completed a scheduled 16 weeks of follow up.

Immunization responses were assessed by measurement of anti-tetanus IgG titers and serum bactericidal antibody titers for serogroup C meningococcal polysaccharide antigen. Measurements were drawn at the start of study participation and at the week 16 visit (4 weeks post-vaccination). Response to tetanus toxoid vaccine was defined as greater than 4 fold increases in anti-tetanus toxoid for subjects with pre-vaccination titers of > 0.1 IU/mL, or ≥ 0.2 IU/mL for subjects with pre-vaccination titers of < 0.1 IU/mL. A secondary endpoint assessed the proportion of subjects with a lower threshold of response (defined as a 2 fold increase from baseline). Response to meningococcal polysaccharide was defined as a serum bactericidal antibody titer of ≥ 8 for serogroup C. Finally, anti-drug antibody results were monitored at subject clinical visits and compared to results from a previous dose-ranging study.

Within each treatment group approximately 84 percent completed the scheduled follow up. Ninety five percent of placebo subjects and 92% of dupilumab subjects were present through week 16 and contributed serologic data.

Moderate to severe injection site reactions occurred in three subjects in the placebo group after Adacel vaccination. No moderate to severe injection site reactions were reported in the dupilumab group. No moderate to severe injection site reactions occurred at the Menomune injection site in any subjects.

**Tetanus toxoid adsorbed vaccine antibody responses**

Adsorbed tetanus toxoid (Adacel) was used to assess T-cell dependent immune response while undergoing dupilumab treatment. Baseline Anti-tetanus IgG levels averaged 1.75 IU/mL in placebo subjects and 1.45 IU/mL in dupilumab subjects with a median of 1.1 in both groups.
Table 17/Table 18: Adacel Responses at Week 16

<table>
<thead>
<tr>
<th></th>
<th>Placebo QW (N=92)</th>
<th>Dupilumab 300 mg QW (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.75 (1.949)</td>
<td>1.45 (1.257)</td>
</tr>
<tr>
<td>Median</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Q1 : Q3</td>
<td>0.67 : 2.12</td>
<td>0.61 : 1.88</td>
</tr>
<tr>
<td>Min : Max</td>
<td>0.0 : 12.1</td>
<td>0.1 : 7.0</td>
</tr>
<tr>
<td>Week 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21.34 (19.147)</td>
<td>18.62 (17.730)</td>
</tr>
<tr>
<td>Median</td>
<td>15.1</td>
<td>13.9</td>
</tr>
<tr>
<td>Q1 : Q3</td>
<td>8.50 : 26.75</td>
<td>8.87 : 19.98</td>
</tr>
<tr>
<td>Min : Max</td>
<td>2.0 : 105.8</td>
<td>1.7 : 101.2</td>
</tr>
<tr>
<td>Change from Baseline to Week 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>19.60 (19.252)</td>
<td>17.17 (17.918)</td>
</tr>
<tr>
<td>Median</td>
<td>13.7</td>
<td>12.6</td>
</tr>
<tr>
<td>Q1 : Q3</td>
<td>6.51 : 24.63</td>
<td>7.26 : 18.63</td>
</tr>
<tr>
<td>Min : Max</td>
<td>0.3 : 105.5</td>
<td>-0.3 : 100.7</td>
</tr>
<tr>
<td>% Change from Baseline to Week 16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3260.24 (6944.193)</td>
<td>3159.89 (9230.999)</td>
</tr>
<tr>
<td>Median</td>
<td>1353.3</td>
<td>1113.6</td>
</tr>
<tr>
<td>Q1 : Q3</td>
<td>423.94 : 2742.92</td>
<td>514.29 : 2924.73</td>
</tr>
<tr>
<td>Min : Max</td>
<td>19.5 : 46022.2</td>
<td>-14.5 : 83945.5</td>
</tr>
<tr>
<td>Number and proportion of patients achieving a positive response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90% CI</td>
<td>(76.01, 89.67)</td>
<td>(75.50, 89.44)</td>
</tr>
<tr>
<td>Difference vs. Placebo (90% CI)</td>
<td>-0.4 (-9.41, 8.69)</td>
<td></td>
</tr>
</tbody>
</table>

Subgroup analysis was performed for body weight, gender, and race with no statistically significant effect on immune responses. In addition a secondary endpoint with a lower threshold for a positive Adacel response (≥ 2 fold increase from baseline) was evaluated with 95.6% and 94.6% positive responses in the placebo and dupilumab groups respectively. The 90% CI of the difference between the two treatment groups was -4.29 to 6.27%.

Historically for both Adacel and Boostrix, tetanus related endpoints for evaluation of immune interference with concomitant vaccine administration have been 4-week post-vaccination anti-tetanus toxoid antibody concentrations (by ELISA) of 0.1 IU/mL and 1 IU/mL, without consideration of pre-vaccination titers. No summary data is presented for the proportion of patients who have met these cutoffs. The individual immune response listings demonstrate that all 92 placebo subjects and 90 dupilumab subjects had titers greater than 1 IU/mL after vaccination. At baseline 2/92 (2.2%) of placebo subjects had a screening anti-tetanus titer of <0.1 IU/mL, and 40/92 (43.5%) of subjects had titers < 1 IU/mL. Similarly, in the
dupilumab group 2/90 (2.2%) and 35/90 (38.9%) subjects had baseline titers <0.1 IU/mL and <1 IU/mL respectively.

Meningococcal vaccine antibody responses

Meningococcal polysaccharide vaccine (Menomune) was used to assess T-cell independent immune response while undergoing dupilumab treatment. Evaluation of serum bactericidal antibody titers (SBA) against serogroup C polysaccharide was performed and evaluated from baseline to week 16. SBA titers ≥ 8 were used as a marker for a positive response. Eighty percent of placebo subjects and 78% of dupilumab subjects achieved a positive response after vaccination.

Table 20/21: Menomune Responses at Week 16

<table>
<thead>
<tr>
<th></th>
<th>Placebo QW (N=92)</th>
<th>Dupilumab 300 mg QW (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>136.6 (636.97)</td>
<td>62.2 (252.70)</td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Q1 : Q3</td>
<td>2.0 : 2.0</td>
<td>2.0 : 2.0</td>
</tr>
<tr>
<td>Min : Max</td>
<td>2 : 4096</td>
<td>2 : 2048</td>
</tr>
<tr>
<td><strong>Week 16</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3066.6 (4707.09)</td>
<td>2942.0 (5032.60)</td>
</tr>
<tr>
<td>Median</td>
<td>1024</td>
<td>1024</td>
</tr>
<tr>
<td>Q1 : Q3</td>
<td>256.0 : 4096.0</td>
<td>256.0 : 4096.0</td>
</tr>
<tr>
<td>Min : Max</td>
<td>2 : 16384</td>
<td>2 : 32768</td>
</tr>
<tr>
<td><strong>Change from Baseline to Week 16</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2930.0 (4612.22)</td>
<td>2879.1 (4993.92)</td>
</tr>
<tr>
<td>Median</td>
<td>1019</td>
<td>1022</td>
</tr>
<tr>
<td>Q1 : Q3</td>
<td>254.0 : 4093.0</td>
<td>254.0 : 4094.0</td>
</tr>
<tr>
<td>Min : Max</td>
<td>-2048 : 16382</td>
<td>0 : 32640</td>
</tr>
<tr>
<td><strong>% Change from Baseline to Week 16</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>92</td>
<td>89</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>102655.978 (174936.5665)</td>
<td>82503.371 (149051.9894)</td>
</tr>
<tr>
<td>Median</td>
<td>25500.00</td>
<td>25500.00</td>
</tr>
<tr>
<td>Q1 : Q3</td>
<td>2300.000 : 1023000000</td>
<td>3100.000 : 1023000000</td>
</tr>
<tr>
<td>Min : Max</td>
<td>-50.00 : 819100.00</td>
<td>0.00 : 819100.00</td>
</tr>
<tr>
<td>Number and proportion of patients achieving a positive response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change from Baseline to Week 16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interpretation of antibody response data

The submitted study presents comparisons of antibody responses to tetanus and meningococcal vaccines in dupilumab treated versus control subjects. No formal non-inferiority endpoints or statistical success criteria were established. However the 90% confidence interval around the difference between the
treatment and placebo groups does exclude a greater than 10% difference in both the tetanus and meningococcal immune response data. Immune interference studies have been used to support concomitant administration of multiple vaccines, although typically with clear hypothesis testing and pre-specified endpoints. Historically measurement of anti-tetanus IgG titers has correlated with protective immune response and a minimal level of 0.1 IU/mL by ELISA has been established as a threshold level conferring protection. Similarly, serum bactericidal antibody has been used as an immunologic surrogate of protection against meningococcal disease, and a SBA reciprocal titer of at least 8 likely confers protection against disease. However it is important to note that no evaluations were made involving the other antigens in the Adacel vaccine, and the above observations cannot be extrapolated to those respective components or other untested vaccines.

Finally, for any claims based on immune response assays it is important to review information on how the assays were validated. The sponsor has not provided this information. We recommended the following information request to the sponsor, in response to which the sponsor provided additional information about the assays (discussed below):

For claims related to evaluation of immune interference between vaccines and concomitantly administered drugs (including other vaccines), FDA requires data to support the validation of assays used to assess post-vaccination immune responses. Please identify the assays used in Study R668-AD-1314 to assess post-vaccination antibody responses to tetanus toxoid (Adacel) and serogroup C meningococcal polysaccharide (Menomune) and clarify whether the validation data for these assays have been submitted to FDA.

Review of Assays (Contributed by Freyja Williams, B.S., CBER/OVRR/DBPAP)

Validation of the anti-tetanus toxoid IgG at

The information provided by the applicant is insufficient to evaluate assay performance. The kit used to determine antibody levels against tetanus toxoid does not appear to have been approved by the FDA for diagnostic use. The information provided by the kit manufacturer also does not provide sufficient information to assess kit performance.

Validation of the meningococcal group C serum bactericidal assay using rabbit complement at the

The validation report provided for the meningococcal serum bactericidal assay for group C included assessment of accuracy based on dilutional linearity and precision. The data in the report are consistent with the four fold variability (median plus or minus one two-fold dilution) expected from this type of assay. However the approach to assessing precision and the analyses are not consistent with currently accepted practices so interpretation of the data is limited.

Review of clinical data

While the information supporting performance of the assays was not adequate for complete review, the data generated during the clinical study were reviewed to determine if any aberrant or unusual data would call into question the interpretation of the immunologic results. As the study was internally controlled, assay performance issues, in particular those related to precision, are mitigated by the study design. In
addition, no endpoint criteria related to the comparison between the study groups were included which simplifies the potential claims that can be made based on the clinical data.

Evaluation of the clinical data describing the responses to the tetanus toxoid and the group C meningococcal polysaccharide did not raise concerns regarding aberrant or unusual data. The responses to the antigens in both groups were very similar based on the overlap of the reverse cumulative distribution curves for each group. Based on the information provided and the clinical results, the label might include a language stating that no substantive differences in immune responses were seen between subjects who received dupilumab prior to immunization when compared to subjects who did not receive dupilumab. No specific claims of non-inferiority or absolute protection in terms of percent above protective thresholds are appropriate.

**Recommendations:**

For the reasons stated above, we concur generally inclusion of these study data in the Drug Interactions section of the Dupixent package insert. Even without definitive evidence of vaccine effectiveness, the benefit/risk balance of using inactivated vaccines as indicated in patients with atopic dermatitis likely remains positive. Practitioners would therefore likely benefit from knowing about the above study, with appropriate clarifying language in regards to the study limitations. We recommend the following revised language for Section 7.2:

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab. After 12 weeks of dupilumab administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®), and antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Tdap and Menomune vaccines were not assessed.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW E WHITE
01/04/2017
CBER/OVRR/DVRPA consult review for BLA 761055. Entered into DARRTS on behalf of Madan Kumar, DO and Doran Fink, MD, PhD.
Date: November 22, 2016 (Updated 12/20/2016)
To: ICCR Lead-Center Contact, Office, Location, E-mail:
CC: Office of Combination Product at: combination@fda.gov

Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Name, Office, E-Mail:
Matthew White, CDER/OMPT/OND/ODEIII/DDDP
Matthew.White@fda.hhs.gov

CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov

Through: Francisco Vicenty, REGO/DMQ/OC, CDRH, WO 66, Rm 3426,
Francisco.Vicenty@fda.hhs.gov
Rakhi Dalal, REGO/DMQ/OC, CDRH, WO 66, Rm 3454,
Rakhi.Dalal@fda.hhs.gov

From: Crystal Lewis, REGO/DMQ/OC, CDRH, WO 66, Rm 3452,
Crystal.lewis@fda.hhs.gov

Applicant/Licensure: Regeneron Pharmaceuticals, Incorporated
777 Old Say Mill River Road, Terry Town
Westchester, NY, 10591
FEI: 1000521995

Submission (Type & Number): BLA761055
Combination Product Name: Dupilumab
Combination Product Intended Use: Atopic Dermatitis
The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant’s compliance with applicable Quality System Requirements for the approvability of BLA761055.

**PRODUCT DESCRIPTION**

Dupilumab drug substance (DS) contains[...](b)(4) The Dupilumab combination product is provided in a single-use prefilled syringe (PFS) that contains 150 mg/mL in a 2mL solution for subcutaneous (SC) injection. An entire PFS of the combination product delivers a 300 mg dose of Dupilumab and is intended for the treatment of atopic dermatitis in adults that is not adequately controlled with topical prescription therapy.

The container closure system for the bulk PFS is the primary packaging for the Dupilumab injectable drug product, see figures 1 and 2 below. Dupilumab bulk PFS consists of:

- 2.25mL clear glass syringe barrel equipped with 27 Gauge (G) ½ inch, [...](b)(4) staked needle, protected by a rigid needle shield.
- [...](b)(4) plunger stopper with [...](b)(4)
REGULATORY HISTORY

The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820 21 CFR part 4.4:

1. Sanofi Winthrop Industrie
   1051 Boulevard Industriel
   Le Trait, France 76580
   FEI #3003259844

Responsibility – This facility is responsible for the manufacture of bulk PFS, PFS and PFS with safety system (PFS-S). The facility is also responsible for release and distribution of PFS and PFS-S; labeling and packaging of PFS and PFS-S. Analytical testing of the bulk PFS and PFS-S; secondary packaging of PFS and PFS-S, and PFS post-approval stability studies also occur at this facility.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 7/7/2016 to 7/19/2016. The inspection covered drugs and was classified OAI.

Inspection Recommendation:
An inspection is required because:
- The firm is responsible for activities related to the manufacturing and/or development of the final combination product and/or the device constituent part and
- A recent medical device inspection of the firm revealed major deficiencies.

**Update 12/20/16:**

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 7/7/2016 to 7/19/2016. The inspection covered drugs and was down-classified to VAI.

**Inspection Recommendation:**
An inspection is not required because:
- A recent medical device inspection of the firm was acceptable.

2. Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, NY 12144-3411
FEI #1000514603

Responsibility – This facility is responsible for the manufacture and control of Dupilumab DS \( (b) (d) \); all DS \( (b) (d) \) in-process testing \( (b) (d) \), in-vitro test for adventitious viruses, \( (b) (d) \) DS, \( (b) (d) \), bulk PFS, PFS-S and PFS release and stability testing; final release site for PFS-S and PFS for distribution. See establishment information, module 1.1.2 for details of testing performed.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 8/15/2016 to 8/19/2016. The inspection covered drugs and was classified VAI.

**Inspection Recommendation:**
An inspection is not required because:
- A recent medical device inspection of the firm was acceptable.

3. Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Rd
Tarrytown, NY 10591-6717
FEI #100051995

Responsibility – This facility is the corporate headquarters for the applicant.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 2/06/2013 to 2/22/2013. This was the first postmarketing adverse drug experience (PADE) inspection for this facility. The inspection was performed in accordance with C.P. 7353001A, Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations and was classified VAI.

**Inspection Recommendation:**
An inspection is not required because:

- A recent medical device inspection of the firm was acceptable.

Responsibility – This facility is responsible for the manufacture of bulk PFS and PFS, labeling and packaging of PFS. This facility is also responsible for the secondary packaging of PFS, and analytical testing site

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 2/06/2013 to 2/22/2013. This was the first postmarketing adverse drug experience (PADE) inspection for this facility. The inspection was performed in accordance with C.P. 7353001A, Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations and was classified VAI.

Inspection Recommendation:
An inspection is not required because:

- A recent medical device inspection of the firm was acceptable.

5. Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Rd
Tarrytown, NY 10591-6717
FEI #1000521995

Responsibility – This facility is the corporate headquarters for the applicant.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 2/06/2013 to 2/22/2013. This was the first postmarketing adverse drug experience (PADE) inspection for this facility. The inspection was performed in accordance with C.P. 7353001A, Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations and was classified VAI.

Inspection Recommendation:
An inspection is not required because:

- A recent medical device inspection of the firm was acceptable.

**DOCUMENTATION REVIEW**
The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

**Management Control, 21 CFR 820.20**
Sanofi has provided documentation for the firm’s quality policies and objectives and established the quality management system. The firm’s policies consist of Management Responsibility, Resource Management, Process Management/Measurement and Analysis/Improvement and can be found in the company’s Quality Manual. Sanofi’s plan for quality utilizes an integrated quality management system and is represented in the firm’s document hierarchy. For additional
information, see Sanofi’s Quality Manual and management reviews located at Sanofi Winthrop Industrie, Le Trait.

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

Update (12/20/16):

Regeneron has stated they have the ultimate responsibility for the overall combination product in the US which include auditing and other oversight activities. 

The information provided by the firm has adequately addressed the requirements of 21 CFR 820.20.

Design Control, General, 21 CFR 820.30
Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality system Requirements showed no deficiencies. No additional information is required for the documentation review.

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

RECOMMENDATION

The application for Dupilumab, BLA761055 is approvable from the perspective of the applicable Quality System Requirements.

1. The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

2. The recommended inspection was conducted and deemed acceptable.

Crystal Lewis -S

Crystal Lewis
Prepared: CLewis: 10/25/16, 12/20/16
Reviewed: RDalal: Month/Day/Year

CTS No.: ICC1600479 and ICC1600557
BLA761055

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year
Month/Day/Year
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/s/

MATTHEW E WHITE
12/21/2016
CDRH/OC/DMQ consult review entered into DARRTS on behalf of Crystal Lewis, CSO, DMQ
PATIENT LABELING REVIEW

Date: December 19, 2016

To: Kendall Marcus, MD
   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)

From: Morgan Walker, PharmD, MBA, CPH
   Patient Labeling Reviewer
   Division of Medical Policy Programs (DMPP)

   Silvia Wanis, PharmD, CPH
   Regulatory Review Officer
   Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)

   Drug Name (established name): Dupixent (dupilumab)

   Dosage Form and Route: injection

   Application Type/Number: BLA 761055

   Applicant: Regeneron Pharmaceuticals, Inc.
1 INTRODUCTION

On July 29, 2016, Regeneron Pharmaceuticals, Inc. submitted the final portion of an
original Biologics License Application (BLA) 761055 for DUPIXENT (dupilumab)
injection for the Agency’s review. The first and second portions of this rolling
submission were submitted on March 31, 2016 and June 29, 2016, respectively. The
proposed indication for DUPIXENT (dupilumab) injection is for the treatment of
adult patients with moderate-to-severe atopic dermatitis whose disease is not
adequately controlled with topical prescription therapies or when those therapies are
not advisable.

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 August 17,
2016, for DMPP and OPDP to review the Applicant’s proposed Patient Package
Insert (PPI) and Instructions for Use (IFU) for DUPIXENT (dupilumab) injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis
(DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

• Draft DUPIXENT (dupilumab) PPI and IFU received on July 29, 2016, and
  received by DMPP and OPDP on November 29, 2016.

• Draft DUPIXENT (dupilumab) injection Prescribing Information (PI) received
  on July 29, 2016, revised by the Review Division throughout the review cycle,
  and received by DMPP and OPDP on November 29, 2016.

• Dupilumab Review of Patient Labeling: IFU and Quick Reference Guide (QRG),
  IND 107969, dated October 19, 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 PPI and IFU 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 reformatted the PPI and IFU documents
using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

• simplified wording and clarified concepts where possible

Reference ID: 4030432
• ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
• removed unnecessary or redundant information
• ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
• ensured that the PPI and IFU meet the criteria as specified in FDA’s Guidance for Useful Written Consumer Medication Information (published July 2006)

The PPI and IFU are acceptable with our recommended changes.

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

Please let us know if you have any questions.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

-------------------------------
BARBARA A FULLER
12/19/2016

SILVIA WANIS
12/19/2016

LASHAWN M GRIFFITHS
12/19/2016
**CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW**

**COA Consult Tracking Number** | AT 2016-200  
---|---
**IND/NDA/BLA Number** | BLA 761055  
**Referenced IND for NDA/BLA** | IND 107969  
**Established Name/Trade Name** | Dupilumab/Dupixent  
**Sponsor/Applicant** | Regeneron Pharmaceuticals, Inc.  
**Indication** | Treatment of moderate-to-severe atopic dermatitis  

**Letter Date/Submission Number** | SDN 4  
**PDUFA Goal Date** | March 29, 2017  
**Date of Consult Request** | September 6, 2016  

**Review Division** | Division of Dermatology and Dental Products  
**Medical Reviewer/Team Leader (TL)** | Brenda Carr, MD  
**Review Division PM** | Matthew White  

**COA Reviewer** | Ebony Dashiell-Aje, PhD  
**COA TL/Secondary Reviewer** | Selena Daniels, PharmD, MS  
**Assoc. Director, COA Staff** | Elektra Papadopoulos, MD  

**Review Completion Date** | December 12, 2016  
**COA Name(s)** | Peak Pruritus NRS  
**COA Type** |  
**Endpoint(s) Concept(s)** | Pruritus intensity  

**Intended Population(s)** | Adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable  

**Please check all that apply:**  
- ☐ Rare Disease/Orphan Designation  
- ☐ Pediatric  

**Note:** This BLA review examined a dossier submission for the Pruritus NRS.
A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) review is provided as a response to a request for consultation by the Division of Dermatology and Dental Products (DDDP) regarding NDA 761055. The Applicant is currently post-phase 3 in their drug development program and awaiting an approval decision from the FDA. The proposed indication is treatment of moderate-to-severe atopic dermatitis.

The Applicant proposed the Peak Pruritus Numeric Rating Scale (NRS) for the measurement of pruritus intensity as a secondary endpoint in their phase 3 clinical trials (R668-AD-1334, R668-AD-1416, and R668-AD-1224) among adult patients whose disease was not adequately controlled with topical prescription therapies or when those therapies were not advisable.

The Division previously deemed the Peak Pruritus NRS acceptable for use as a secondary endpoint to assess clinical benefit in their phase 3 trials (see Meeting Minutes dated May, 22, 2014; Reference ID: 3515910). Additionally, there was agreement on the peak pruritus responder definition – the proportion of participants with improvement greater than or equal to the responder threshold on the Peak Pruritus NRS.

Therefore, the review focused on whether the Peak Pruritus NRS was fit-for-purpose in the context of this particular drug development program to assess symptoms of atopic dermatitis in clinical trials. The clinical review provides further details of the study designs.

This review concludes that based on qualitative and quantitative evidence presented in the Patient-reported outcome (PRO) Evidence Dossier, the Peak Pruritus NRS appropriately measures patient-reported pruritus intensity and appears to be fit-for purpose for this drug development program.

B. BACKGROUND

During the End-of-phase 2 meeting held on May 21, 2014, the Agency agreed that pruritus was an important concept to measure among patients with atopic dermatitis and that the Peak Pruritus NRS was suitable as a secondary endpoint to measure this concept in the Applicant’s phase 3 trials (see Meeting Minutes dated May, 22, 2014; Reference ID: 3515910). This advice was also conveyed in a subsequent advice letter (dated October 27, 2014; Reference ID 3648520). The measurement of pruritus intensity based on the Peak Pruritus NRS was supported by data from their phase 2b study (R668-AD-1021) and was confirmed as an appropriate key secondary endpoint in their phase 3 studies (R668-AD-1334, R668-AD-1416, and R668-AD-1224).
Clinical Outcome Assessment Review
Ebony Dashiell-Aje, PhD
BLA 761055
Dupilumab/Dupixent
Pruritus NRS

Additional Agency feedback was provided on October 20, 2015 (Reference ID 3835992) regarding the final SAPs for studies R668-AD-1334, R668-AD-1416, and R668-AD-1224 and the Agency confirmed the appropriateness of the responder definition – the proportion of participants with improvement greater than or equal to the responder threshold on the Peak Pruritus NRS.

Materials reviewed:

- PRO evidence dossier (including qualitative study report and interview transcripts, and psychometric evaluation report)
- Applicant’s responses to Agency’s information requests for post-hoc exploratory analysis (i.e., CDF plots)
- Clinical study reports (for studies R668-AD-1021, R668-AD-1334, R668-AD-1416, and R668-AD-1224)
- Previous COA Reviews during IND 107969 phase:
  - AT 2012-154; Voqui (Reference ID: 3243826), finalized in DARRTS on January 11, 2013

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 CONTEXT OF USE

1.1 Clinical Trial Population
Adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

1.2 Endpoint Hierarchy and Definition
The Peak Pruritus NRS was designated as a secondary endpoint in the phase 2b and phase 3 trials, defined as the proportion of participants with improvement greater than or equal to the responder threshold on the Peak Pruritus NRS.
2 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK
The concept of interest for the Peak Pruritus NRS is pruritus intensity at its worst.

[Reviewer’s comment: The Agency agreed that pruritus was an important concept to measure among patients with atopic dermatitis and that the pruritus NRS was suitable as a secondary endpoint to measure this concept in the Applicant’s phase 3 trials (see Meeting Minutes dated May, 22, 2014; Reference ID: 3515910).]

3 CLINICAL OUTCOME ASSESSMENTS
The Peak Pruritus NRS is a single self-administered item that assesses pruritus intensity (at its worst) during the previous 24 hours. The single item is rated using an 11-point NRS in which 0 = No itch and 10 = Worst itch imaginable and can be found in Appendix A.

4 CONTENT VALIDITY
In line with recommendations from the FDA’s PRO Guidance for Industry\(^1\), the Peak Pruritus NRS was developed through a review of the literature and qualitative research. Early in the clinical development program, the Applicant conducted a review of published literature and gathered input from adult patients with atopic dermatitis (one-on-one interviews). The qualitative sample consisted of 14 English-speaking patients who were recruited from two United States (U.S.) geographic locations: Detroit, Michigan (n = 6), and Tampa, Florida (n = 8). Within the qualitative sample, 64% were women, while the mean age of all participants was 40 years (SD 15.2, range 19-71 years). The majority of patients were Caucasian (n= 7/14, 50%), and the remaining racial/ethnic groups were African American/Black (n= 4/14, 29%), and Hispanic (n=3/14. 21%).

Patient interviews were conducted in-person and consisted of hybrid concept elicitation and cognitive debriefing elements. During the interviews, patients were asked both open-ended questions – to elicit relevant symptoms and impacts of atopic dermatitis (including their experience with itch related to their condition), and targeted questions about the PRO item content (that the question was understandable and that the instructions and response options made sense and were meaningful to the patients). Two versions of the pruritus NRS (worst [peak] and average) were compared to determine which version was preferred by patients. Interview results revealed that a majority of patients (n = 13/14, 93%) spontaneously discussed pruritus as a salient symptom of their atopic dermatitis; all participants (n=14) reported experiencing pruritus as a symptom of their condition. When given the two versions of the NRS


Reference ID: 4027778
(worst [peak] and average itch), patients had a more precise interpretation of the worst (peak) pruritus question. A majority of patients (n = 11/14, 79%) also stated that the concept of worst itch was easier to recall and rate than the average itch question. Patients indicated that they would be able to complete the Peak Pruritus NRS daily via an automated phone system over a period of 4 months without difficulty.

[Reviewer’s comments: The findings from the Applicant’s literature review and concept elicitation/cognitive interviews support the assertion that pruritus is a core symptom of atopic dermatitis. In general, patients appeared to prefer the Peak Pruritus NRS and were able to understand and interpret the final scale instructions, item wording, response options, and recall period appropriately.

It should be noted that pruritus severity levels of the qualitative sample were not reported. Likewise, interviews were only conducted among a U.S. sample and eligibility status was determined based on self-reports of physician diagnosis. Due to face validity and general acceptability of the pruritus NRS for measuring pruritus intensity in atopic dermatitis, this reviewer still deems this scale appropriate and views the qualitative evidence presented in the dossier as supportive of the content validity in this target patient population.]

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

The Applicant evaluated the psychometric properties of the Peak Pruritus NRS using two data sets based on approved, *a priori* psychometric analysis plans where exploratory analyses were conducted using phase 2b data (Study R668-AD-1021), and confirmatory analyses were conducted using pooled phase 3 data (Studies R668-AD-1334 and R668-AD-1416). Results indicated an acceptable level of evidence to support the reliability and validity of the scale. A summary of the psychometric evaluation results from these analyses are summarized in the table below.
Table 2. Summary of Key Measurement Properties of the Peak Pruritus NRS

<table>
<thead>
<tr>
<th>Measurement Property</th>
<th>Phase 2b Study (R668-AD-1021) (n = 379)</th>
<th>Pooled Phase 3 Monotherapy Studies (R668-AD-1334, R668-AD-1416) (n = 1,379)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional measure properties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response distribution</td>
<td>Proportion (%) with lowest itch category (0)</td>
<td>Proportion (%) with highest itch category (10)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Week 16</td>
<td>4.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Mean (SD), median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>6.69 (1.93), 6.66</td>
<td>7.39 (1.83), 7.71</td>
</tr>
<tr>
<td>Week 16</td>
<td>3.94 (2.43), 2.67</td>
<td>4.15 (2.51), 4.00</td>
</tr>
<tr>
<td>Convergent validity</td>
<td>Pearson correlation coefficient with Peak Pruritus NRS at baseline, r (n)</td>
<td></td>
</tr>
<tr>
<td>SCIDRAD itch VAS</td>
<td>0.77* (n = 369)</td>
<td>0.72* (n = 1263)</td>
</tr>
<tr>
<td>DLQI itch item</td>
<td>0.67* (n = 369)</td>
<td>0.61* (n = 1374)</td>
</tr>
<tr>
<td>PCS</td>
<td>0.75* (n = 369)</td>
<td>0.66* (n = 1374)</td>
</tr>
<tr>
<td>EASI</td>
<td>0.09 (n = 369)</td>
<td>0.21* (n = 1373)</td>
</tr>
<tr>
<td>DIA</td>
<td>0.17* (n = 369)</td>
<td>0.24* (n = 1373)</td>
</tr>
<tr>
<td>Known-groups validity</td>
<td>Mean Peak Pruritus NRS scores per known group at Week 16</td>
<td></td>
</tr>
<tr>
<td>DLQI bands (no impact, extremely large impact)</td>
<td>1.94, 7.63</td>
<td>2.86, 7.51</td>
</tr>
<tr>
<td>PGDQ (poor, excellent)</td>
<td>5.97, 2.10</td>
<td>6.60, 1.61</td>
</tr>
<tr>
<td>Longitudinal measurement properties</td>
<td>Test-retest reliability</td>
<td></td>
</tr>
<tr>
<td>ICC (95%) at prespecified timepoints*</td>
<td>0.95 (0.94, 0.96), n = 323</td>
<td>0.96 (0.95, 0.96), n = 1272</td>
</tr>
<tr>
<td>Sensitivity to change in Peak Pruritus NRS score from baseline to week 16 (SD units)</td>
<td>-2.67 (2.35), -2.42, -3.24 (2.92), -3.07</td>
<td></td>
</tr>
<tr>
<td>Effect size of change from baseline to week 16 (SD units)</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Standardized response mean (SD change units)</td>
<td>-1.1</td>
<td>-1.3</td>
</tr>
<tr>
<td>Pearson correlation coefficient with Peak Pruritus NRS (change from baseline), r (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCIDRAD itch VAS</td>
<td>0.77* (n = 320)</td>
<td>0.73* (n = 1259)</td>
</tr>
<tr>
<td>DLQI itch item</td>
<td>0.66* (n = 320)</td>
<td>0.64* (n = 1273)</td>
</tr>
<tr>
<td>PCS</td>
<td>0.71* (n = 321)</td>
<td>0.72* (n = 1280)</td>
</tr>
<tr>
<td>EASI</td>
<td>0.50* (n = 321)</td>
<td>0.46* (n = 1273)</td>
</tr>
<tr>
<td>DIA</td>
<td>0.50* (n = 321)</td>
<td>0.46* (n = 1273)</td>
</tr>
</tbody>
</table>

* P < 0.01, Pearson correlation coefficients.

Reviewer’s comments: Results from the phase 2b (R668-AD-1021) analyses indicate that the Peak Pruritus NRS is a reliable and valid measure that is discriminating and able to detect change over time. These results were confirmed in analyses conducted on the pooled phase 3 trial data (R668-AD-1334 and R668-AD-1416). This evidence, along with the qualitative study
results, suggests that the Peak Pruritus NRS is a well-defined and reliable measure of pruritus intensity in adult patients with moderate-to-severe atopic dermatitis.

6 INTERPRETATION OF SCORES

The Applicant proposed a ≥ 4-point threshold of meaningful change for the Peak Pruritus NRS and generated cumulative distribution function (CDF) plots depicting between group differences from baseline to week 16 using phase 2b data (R668-AD-1021; overall sample). Results from their analyses revealed a greater proportion of patients in the dupilumab treatment arms achieved ≥ 4 point improvement (negative change) in pruritus from baseline to week 16 when compared to placebo.

The Applicant also generated evidence to support their proposed threshold using a qualitative approach. During the qualitative interviews, patients were asked to report what the smallest clinically meaningful change on the NRS would be within the context of a new treatment. Results indicated that most patients (10/14 = 71%) considered at least a 2-point change to be a meaningful improvement. Of the remaining participants, one patient reported a minimum 1-point change to be meaningful, two reported at least a 3-point change and one patient reported that only a change of at least 4 points would be meaningful.

To further aid in results interpretation, the following additional CDF plots depicting within-patient change were requested:

- For the Pruritus NRS (separately for the overall sample and the GE4 sample with baseline peak pruritus NRS of at least 4)
  - CDF plot of Pruritus NRS change scores from baseline to Week 16 for all patients (both treatment and placebo arms pooled) by the different PCS response options at Week 16
  - CDF plot of change scores from baseline to Week 16 for all patients (both treatment and placebo arms pooled) by the PCS change scores (differences) between baseline and Week 16 (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.)

[Reviewer’s comment: The additional CDF plots were received November 3, 2016. Results were supportive of the proposed threshold of ≥ 4 point improvement on the Peak Pruritus NRS.]

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

No documentation has been provided on translation and cultural adaptation of the Peak Pruritus NRS.

[Reviewer’s comment: No documentation has been provided on cross-cultural equivalence. If the Applicant will be using this measure outside the US, it is recommended to translate and culturally adapt this measure per best practices.]
8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

Patients were trained to record their Peak Pruritus NRS ratings using an interactive voice response system (IVRS) at the screening visit. Patients completed the rating scale daily through week 16 and weekly thereafter through the last study visit. Clinical sites received alerts when patients did not complete IVRS items and were expected to contact patients who had missed two consecutive IVRS entries to encourage patient compliance.

[Reviewer’s comment: Training materials, including Peak Pruritus NRS administration instructions, were presented for review in the PRO dossier. These instructions appear clear and comprehensive, allowing for completion of the scale as intended.]

9 KEY REFERENCES FOR COA

APPENDIX A. PEAK PRURITUS NRS

Figure 1. Peak Pruritus NRS

On a scale of 0 to 10, with 0 being “no itch” and 10 being “worst itch imaginable”, how would you rate your itch at the worst moment during the previous 24 hours?

<table>
<thead>
<tr>
<th>No itch</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Worst itch imaginable</th>
</tr>
</thead>
</table>

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/s/

EBONY N DASHIELL-AJE  
12/14/2016

SELENA R DANIELS  
12/14/2016

ELEKTRA J PAPADOPOULOS  
12/14/2016
Memorandum

Date: December 14, 2016

To: Snezana Trajkovic, CTL
Division of Dermatology and Dental Products (DDDP)

Brenda Carr, Medical Officer
DDDP

Matthew White
Regulatory Project Manager
DDDP

From: Silvia Wanis, PharmD, CPH
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 761055
OPDP labeling comments for DUPIXENT® (dupilumab) injection, for subcutaneous use

On August 17, 2016, DDDP consulted OPDP to review the proposed Package Insert (PI), Patient Package Insert (PPI), Carton/Container Labeling, and Instructions For Use (IFU) for DUPIXENT® (dupilumab) injection, for subcutaneous use (Dupixent).

OPDP’s comments on the proposed labeling, which are based on the draft version of the PI emailed by Matthew White on November 29, 2016, are provided below.

OPDP has no further comments on the proposed Carton/Container Labeling, which is based on the draft version emailed by Matthew White on December 14, 2016.

OPDP’s review and comments on the proposed PPI and IFU were conducted jointly with the Division of Medical Policy Programs (DMPP). The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the Medication Guide and Instruction for Use under separate cover.
If you have any questions, please feel free to contact me:

Silvia Wanis: 301-796-5198; silvia.wanis@fda.hhs.gov

Thank you! OPDP appreciates the opportunity to provide comments on these materials.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SILVIA WANIS
12/14/2016
DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date: November 22, 2016

To: ICCR Lead-Center Contact, Office, Location, E-mail:

CC: Office of Combination Product at: combination@fda.gov
Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Name, Office, E-Mail:
Matthew White, CDER/OMPT/OND/ODEIII/DDDP
Matthew.White@fda.hhs.gov

Through: Francisco Vicenty, REGO/DMQ/OC, CDRH, WO 66, Rm 3426,
Francisco.Vicenty@fda.hhs.gov
Rakhi Dalal, REGO/DMQ/OC, CDRH, WO 66, Rm 3454,
Rakhi.Dalal@fda.hhs.gov

From: Crystal Lewis, REGO/DMQ/OC, CDRH, WO 66, Rm 3452,
Crystal.lewis@fda.hhs.gov

Applicant/Licensee: Regeneron Pharmaceuticals, Incorporated
777 Old Say Mill River Road, Terry Town
Westchester, NY, 10591
FEI: 1000521995

Submission (Type & Number):
BLA761055

Combination Product Name: Dupilumab
Combination Product Intended Use: Atopic Dermatitis

Reference ID: 4024059
The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant’s compliance with applicable Quality System Requirements for the approvability of BLA761055.

**PRODUCT DESCRIPTION**

Dupilumab drug substance (DS) combination product is provided in a single-use prefilled syringe (PFS) that contains 150 mg/mL in a 2mL solution for subcutaneous (SC) injection. An entire PFS of the combination product delivers a 300 mg dose of Dupilumab and is intended for the treatment of atopic dermatitis in adults that is not adequately controlled with topical prescription therapy.

The container closure system for the bulk PFS is the primary packaging for the Dupilumab injectable drug product, see figures 1 and 2 below. Dupilumab bulk PFS consists of:

- 2.25mL clear glass syringe barrel equipped with 27 Gauge (G) ½ inch, staked needle, protected by a rigid needle shield.
- (b) (4) plunger stopper
REGULATORY HISTORY
The following facilities were identified as being subject to applicable Quality System Requirements under 21 CFR part 820 21CFR part 4.4:

1. Sanofi Winthrop Industrie
   1051 Boulevard Industriel
   Le Trait, France 76580
   FEI #3003259844

Responsibility –This facility is responsible for the manufacture of bulk PFS, PFS and PFS with safety system (PFS-S). The facility is also responsible for release and distribution of PFS and PFS-S; labeling and packaging of PFS and PFS-S. Analytical testing of the bulk PFS and PFS-S; secondary packaging of PFS and PFS-S, and PFS post-approval stability studies also occur at this facility.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 7/7/2016 to 7/19/2016. The inspection covered drugs and was classified OAI.

Inspection Recommendation:
An inspection is required because:
- The firm is responsible for activities related to the manufacturing and/or development of the final combination product and/or the device constituent part and
- A recent medical device inspection of the firm revealed major deficiencies.

2. Regeneron Pharmaceuticals, Inc.
   81 Columbia Turnpike
   Rensselaer, NY 12144-3411
   FEI #1000514603

Responsibility – This facility is responsible for the manufacture and control of Dupilumab DS; all DS and in-process testing in vitro test for adventitious viruses, DS bulk PFS, PFS-S and PFS release and stability testing; final release site for PFS-S and PFS for distribution. See establishment information, module 1.1.2 for details of testing performed.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 8/15/2016 to 8/19/2016. The inspection covered drugs and was classified VAI.

Inspection Recommendation:
An inspection is not required because:
- A recent medical device inspection of the firm was acceptable.

3. Regeneron Pharmaceuticals, Inc.
   777 Old Saw Mill River Rd
   Tarrytown, NY 10591-6717
   FEI #1000521995

Responsibility – This facility is the corporate headquarters for the applicant.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 2/06/2013 to 2/22/2013. This was the first postmarketing adverse drug experience (PARE) inspection for this facility. The inspection was performed in accordance with C.P. 7353001A, Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations and was classified VAI.

Inspection Recommendation:
An inspection is not required because:
- A recent medical device inspection of the firm was acceptable.

4. FEI # (b) (4)

Responsibility – This facility is responsible for the manufacture of bulk PFS and PFS, labeling and packaging of PFS. This facility is also responsible for the secondary packaging of PFS, and analytical testing site.

Reference ID: 4024059
Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on \( b(4) \). The inspection covered drugs and devices and was classified VAI.

**Inspection Recommendation:**
An inspection is not required because:
- A recent medical device inspection of the firm was acceptable.

5. Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Rd
Tarrytown, NY 10591-6717
FEI #1000521995

Responsibility – This facility is the corporate headquarters for the applicant.

Inspectional History – An analysis of the firm’s inspection history over the past 2 years revealed an inspection was conducted on 2/06/2013 to 2/22/2013. This was the first postmarketing adverse drug experience (PADE) inspection for this facility. The inspection was performed in accordance with C.P. 7353001A, Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations and was classified VAI.

**Inspection Recommendation:**
An inspection is not required because:
- A recent medical device inspection of the firm was acceptable.

**DOCUMENTATION REVIEW**
The application was searched for documents pertaining to applicable 21 CFR part 820 regulations for this combination product.

**Management Control, 21 CFR 820.20**

(b)(4)

The information provided by the firm has inadequately addressed the requirements of 21 CFR 820.20.

**Design Control, General, 21 CFR 820.30**

(b)(4)
**Documentation Review Recommendation**
Additional information is required for an adequate documentation review.

**Deficiency to be conveyed to the applicant**
The following deficiency has been identified while doing the documentation review of application Dupilumab—#BLA761055 in reference to applicable 21 CFR 820 regulations and manufacturing of the finished combination product:

1. The submission did not include information addressing which firm has ultimate responsibility for the overall combination product.

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

**RECOMMENDATION**
The approvability of application for Dupilumab—#BLA761055 should be delayed for the following reasons:
(1) A deficiency was identified during the documentation review. Additional information from the firm is needed to complete the documentation review.

(2) A pre-approval inspection is recommended for the following facility:

a. Sanofi Winthrop Industrie
   1051 Boulevard Industriel
   Le Trait, France 76580
   FEI #3003259844

Prepared: CLewis: 10/25/16
Reviewed: RDalal: Month/Day/Year

CTS No.: ICC1600479 and ICC1600557
BLA761055

Review Cycle Meeting Attendance:
Month/Day/Year
Month/Day/Year
Month/Day/Year

Reference ID: 4024059
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW E WHITE
12/07/2016
CDRH/OC/DMQ consult review entered into DARRTS on behalf of Crystal Lewis, REGO/DMQ/OC, CDRH

Reference ID: 4024059
Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

**Application:** BLA 761055

**Application Type:** New BLA

**Drug Name(s)/Dosage Form(s):** Dupixent (dupilumab) injection, 150 mg/mL

**Applicant:** Regeneron Pharmaceuticals, Inc.

**Receipt Date:** 7-29-2016

**Goal Date:** 3-29-2016

1. Regulatory History and Applicant’s Main Proposals

DUPIXENT (dupilumab) injection is a human interleukin-4 and interleukin-13 antagonist indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical [b](4)

Dupilumab was granted designation as a breakthrough therapy on 11-18-2014 under IND 107969.

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 of Prescribing Information (SRPI)” checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.
4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-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 for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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:

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. 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:

3. A horizontal line must separate:
   - HL from the Table of Contents (TOC), and
   - TOC from the Full Prescribing Information (FPI).

   Comment:

4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be bolded and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

   Comment:

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 for HL format.

   Comment:

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:

7. Headings in HL must be presented in the following order:

<table>
<thead>
<tr>
<th>Heading</th>
<th>Required/Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Highlights Heading</td>
<td>Required</td>
</tr>
<tr>
<td>• Highlights Limitation Statement</td>
<td>Required</td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

- **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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

**HIGHLIGHTS DETAILS**

**Highlights Heading**

YES 8. At the beginning of HL, the following heading, “HIGHLIGHTS OF PRESCRIBING INFORMATION” must be **bolded** and should appear in all UPPER CASE letters.

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 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 title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term “**WARNING**” and not “**WARNINGS**” should be used. For example: “**WARNING: SERIOUS**
Selected Requirements of Prescribing Information

INFECTIONS and ACUTE HEPATIC FAILURE”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title 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 must be placed immediately beneath the BW title, and should be centered 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 title 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 five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015.”

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word “None.”

Comment:
Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch].”

**Comment:**

Patient Counseling Information Statement in Highlights

22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

- If a product **does not** have FDA-approved patient labeling:
  - See 17 for PATIENT COUNSELING INFORMATION

- If a product **has (or will have)** FDA-approved patient labeling:
  - See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling
  - See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

**Comment:**

Revision Date in Highlights

23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “Revised: 8/2015”).

**Comment:**
## Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

<table>
<thead>
<tr>
<th>Requirement</th>
<th>YES</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>24. The TOC should be in a two-column format.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. 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 <strong>bolded</strong>.</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in <strong>bolded</strong>.</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>27. In the TOC, all section headings must be <strong>bolded</strong> and should be in UPPER CASE.</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>28. 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 (for, of, to) and articles (a, an, the), or conjunctions (or, and)].</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”</td>
<td>YES</td>
<td></td>
</tr>
</tbody>
</table>
Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

31. 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 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use “Labor and Delivery”)
    8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use “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:

32. 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)].”

**Comment:**
Selected Requirements of Prescribing Information

33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading “FULL PRESCRIBING INFORMATION” must be bolded, must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be bolded.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word “WARNING” and other words to identify the subject of the warning. (Even if there is more than one warning, the term, “WARNING” and not “WARNINGS” should be used.) For example: “WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE.” If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

“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 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), 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 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) 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: Highlights and Table of Contents Format**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

**PROPRIETARY NAME** (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

**WARNING: TITLE OF WARNING**
See full prescribing information for complete boxed warning.
- Text (4)
- Text (5.x)

**RECENT MAJOR CHANGES**
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

**INDICATIONS AND USAGE**
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for ... (1)

Limitations of Use: Text (1)

**DOSSAGE AND ADMINISTRATION**
- Text (2.x)
- Text (2.x)

**DOSE FORMS AND STRENGTHS**
Dosage form(s); strength(s) (3)

**CONTRAINDICATIONS**
- Text (4)
- Text (4)

**WARNINGS AND PRECAUTIONS**
- Text (5.x)
- Text (5.x)

**ADVERSE REACTIONS**
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**
- Text (7.x)

**USE IN SPECIFIC POPULATIONS**
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

**FULL PRESCRIBING INFORMATION: CONTENTS**

1 WARNING: TITLE OF WARNING
2 INDICATIONS AND USAGE
3 DOSAGE AND ADMINISTRATION
4 7 DRUG INTERACTIONS
5 DOSAGE FORMS AND STRENGTHS
6 CONTRAINDICATIONS
7 WARNINGS AND PRECAUTIONS
8 ADVERSE REACTIONS
9 DRUG ABUSE AND DEPENDENCE
10 CLINICAL PHARMACOLOGY
11 USE IN SPECIFIC POPULATIONS
12 OVERDOSAGE
13 NONCLINICAL TOXICOLOGY
14 DESCRIPTION
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MATTHEW E WHITE
09/13/2016
Signed on behalf of Barbara Gould, Chief, Project Management Staff

Reference ID: 3985208
**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

<table>
<thead>
<tr>
<th>BLA#</th>
<th>NDA Supplement #: S-</th>
<th>BLA Supplement #: S-</th>
<th>Efficacy Supplement Category:</th>
</tr>
</thead>
<tbody>
<tr>
<td>761055</td>
<td></td>
<td></td>
<td>□ New Indication (SE1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>□ New Dosing Regimen (SE2)</td>
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<td>□ New Route Of Administration (SE3)</td>
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<td>□ Comparative Efficacy Claim (SE4)</td>
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<td>□ New Patient Population (SE5)</td>
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<td>□ Rx To OTC Switch (SE6)</td>
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<td></td>
<td>□ Accelerated Approval Confirmatory Study (SE7)</td>
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<td></td>
<td>□ Labeling Change With Clinical Data (SE8)</td>
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<td></td>
<td></td>
<td></td>
<td>□ Manufacturing Change With Clinical Data (SE9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>□ Animal Rule Confirmatory Study (SE10)</td>
</tr>
</tbody>
</table>

Proprietary Name: Dupixent  
Established/Proper Name: Dupilumab  
Dosage Form: Solution for injection  
Strengths: 150 mg/mL

<table>
<thead>
<tr>
<th>Applicant: Regeneron Pharmaceuticals, Inc.</th>
<th>Agent for Applicant (if applicable): N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of Application: 7-29-16</td>
<td>Date of Receipt: 7-29-16</td>
</tr>
<tr>
<td>Date of Filing Meeting: 9-2-16</td>
<td>Date clock started after Unacceptable for Filing (UN): N/A</td>
</tr>
<tr>
<td>PDUFA/BsUFA Goal Date: 3-29-17</td>
<td>Action Goal Date (if different): N/A</td>
</tr>
<tr>
<td>Filing Date: 9-27-16</td>
<td>Date of Filing Meeting: 9-2-16</td>
</tr>
</tbody>
</table>

Chemical Classification (original NDAs only):  
□ Type 1- New Molecular Entity (NME); NME and New Combination  
□ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination  
□ Type 3- New Dosage Form; New Dosage Form and New Combination  
□ Type 4- New Combination  
□ Type 5- New Formulation or New Manufacturer  
□ Type 7- Drug Already Marketed without Approved NDA  
□ Type 8- Partial Rx to OTC Switch  
□ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval)  
□ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)

Proposed indication(s): For the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupilumab can be used with or without topical .

Type of Original NDA:  
AND (if applicable)  

Type of NDA Supplement:  

If 505(b)(2)NDA/NDA Supplement: Draft the “505(b)(2) Assessment” review found at:

<table>
<thead>
<tr>
<th>Type of Original NDA:</th>
<th>505(b)(1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>505(b)(2)</td>
<td>505(b)(1)</td>
</tr>
<tr>
<td>505(b)(2)</td>
<td>505(b)(2)</td>
</tr>
</tbody>
</table>
### Type of BLA

If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team

<table>
<thead>
<tr>
<th>Review Classification:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The application will be a priority review if:</td>
</tr>
<tr>
<td>• 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)</td>
</tr>
<tr>
<td>• The product is a Qualified Infectious Disease Product (QIDP)</td>
</tr>
<tr>
<td>• A Tropical Disease Priority Review Voucher was submitted</td>
</tr>
<tr>
<td>• A Pediatric Rare Disease Priority Review Voucher was submitted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of BLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒ 351(a)</td>
</tr>
<tr>
<td>☐ 351(k)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resubmission after withdrawal?</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
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</table>

<table>
<thead>
<tr>
<th>Resubmission after refuse to file?</th>
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</thead>
<tbody>
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<td>☐</td>
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<table>
<thead>
<tr>
<th>Part 3 Combination Product?</th>
</tr>
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<tbody>
<tr>
<td>☒</td>
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</tbody>
</table>

If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults

<table>
<thead>
<tr>
<th>Convenience kit/Co-package</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Pre-filled drug delivery device/system (syringe, patch, etc.)</td>
</tr>
<tr>
<td>☒</td>
</tr>
<tr>
<td>Pre-filled biologic delivery device/system (syringe, patch, etc.)</td>
</tr>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Device coated/impregnated/combined with drug</td>
</tr>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Device coated/impregnated/combined with biologic</td>
</tr>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Separate products requiring cross-labeling</td>
</tr>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Drug/Biologic</td>
</tr>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Possible combination based on cross-labeling of separate products</td>
</tr>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Other (drug/device/biological product)</td>
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<td>☐</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Fast Track Designation</th>
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<td>☒</td>
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</table>

Breakthrough Therapy Designation (set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)

<table>
<thead>
<tr>
<th>Rapid Review</th>
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<table>
<thead>
<tr>
<th>Orphan Designation</th>
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<tbody>
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</table>

<table>
<thead>
<tr>
<th>Rx-to-OTC switch, Full</th>
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</thead>
<tbody>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Rx-to-OTC switch, Partial</td>
</tr>
<tr>
<td>☐</td>
</tr>
<tr>
<td>Direct-to-OTC</td>
</tr>
<tr>
<td>☐</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Other:</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Collaborative Review Division (if OTC product):</th>
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<tbody>
<tr>
<td>N/A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>List referenced IND Number(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>IND 107969</td>
</tr>
</tbody>
</table>

### Goal Dates/Product Names/Classification Properties

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PDUFA/BsUFA and Action Goal dates correct in the electronic archive?

If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.

Are the established/proper and applicant names correct in electronic archive?

Reference ID: 3986410
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 electronic archive.

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)? Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: [http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm](http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm)

If no, ask the document room staff to make the appropriate entries.

<table>
<thead>
<tr>
<th>Application Integrity Policy</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application affected by the Application Integrity Policy (AIP)? Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If yes, explain in comment column.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If affected by AIP, has OC been notified of the submission? If yes, date notified:</td>
<td>☐</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>User Fees</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?</td>
<td>☒</td>
<td>☐</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**User Fee Status**

*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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.*

- Payment for this application (check daily email from UserFeeAR@fda.hhs.gov):
  - ☒ Paid
  - ☐ Exempt (orphan, government)
  - ☐ Waived (e.g., small business, public health)
  - ☐ Not required

- Payment of other user fees:
  - ☒ Not in arrears
  - ☐ In arrears

**User Fee Bundling Policy**


**505(b)(2)**

<table>
<thead>
<tr>
<th>505(b)(2)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
</table>

Reference ID: 3986410
<table>
<thead>
<tr>
<th>(NDAs/NDA Efficacy Supplements only)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the application a 505(b)(2) NDA? (Check the 356h form, cover letter, and annotated labeling). <strong>If yes</strong>, answer the bulleted questions below:</td>
<td>☐ ☒</td>
</tr>
<tr>
<td>• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</td>
<td>☐ ☐</td>
</tr>
<tr>
<td>• 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)].</td>
<td>☐ ☐</td>
</tr>
<tr>
<td>• 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)]?</td>
<td>☐ ☐</td>
</tr>
</tbody>
</table>

*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.*

| • Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? | ☐ ☐ |

*Check the Electronic Orange Book at:*

http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

*If yes, please list below:*

<table>
<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>
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</tbody>
</table>

*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 orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.*

<table>
<thead>
<tr>
<th>Exclusivity Designations and Approvals list at:</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Check the Orphan Drug Designations and Approvals list at:</td>
<td>☐</td>
<td>☒</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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)]?*  
*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? | ☐ | ☒ | ☐ |

*If yes, # years requested:*
**Note:** An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

**NDAs only:** Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?  

<p>| | | |</p>
<table>
<thead>
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</table>

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)?

If yes, contact the Orange Book Staff (CDER-Orange Book Staff).

**BLAs only:** Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?

If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager

**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.

---

### Format and Content

*Do not check mixed submission if the only electronic component is the content of labeling (COL).*

<table>
<thead>
<tr>
<th></th>
<th>All paper (except for COL)</th>
<th>All electronic</th>
<th>Mixed (paper/electronic)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☒</td>
<td></td>
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</tr>
</tbody>
</table>

If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?

<table>
<thead>
<tr>
<th>Overall Format/Content</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>If electronic submission, does it follow the eCTD guidance?¹</td>
<td>☒</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If not, explain (e.g., waiver granted).</td>
<td></td>
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</tr>
<tr>
<td>Index: Does the submission contain an accurate comprehensive index?</td>
<td>☒</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>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:</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

If no, explain.

**BLAs only**: Companion application received if a shared or divided manufacturing arrangement?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐</td>
<td>☑</td>
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</tbody>
</table>

If yes, BLA #

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>

### Forms and Certifications

**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.

#### Application Form

Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>

*If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].*

Are all establishments and their registration numbers listed on the form/attached to the form?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>☑</td>
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</tbody>
</table>

#### Patent Information

**(NDAs/NDA efficacy supplements only)**

Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
<td>☐</td>
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</tbody>
</table>

#### Financial Disclosure

Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>☑</td>
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</tbody>
</table>

*Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*

**Note**: Financial disclosure is required for bioequivalence studies that are the basis for approval.

#### Clinical Trials Database

Is form FDA 3674 included with authorized signature?

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</thead>
<tbody>
<tr>
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</tbody>
</table>

*If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”

Included in the first rolling submission under SDN 1.
### Debarment Certification

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td>❌</td>
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</table>

**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].

**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…”

### Field Copy Certification (NDAs/NDA efficacy supplements only)

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</table>

**For paper submissions only:** Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?

**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)**

**If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.**

### Controlled Substance/Product with Abuse Potential

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</table>

**For NMEs:**
Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?

**If yes, date consult sent to the Controlled Substance Staff:**

**For non-NMEs:**
Date of consult sent to Controlled Substance Staff:

### Pediatrics

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
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</table>

### PREA

<table>
<thead>
<tr>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td>❌</td>
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</table>

**If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting**

---

**Reference ID: 3986410**
**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 pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.

<table>
<thead>
<tr>
<th><strong>If the application triggers PREA,</strong> is there an agreed Initial Pediatric Study Plan (iPSP)?</th>
<th>☑</th>
<th>☐</th>
<th>☐</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>If no, may be an RTF issue - contact DPMH for advice.</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>If required by the agreed iPSP,</strong> are the pediatric studies outlined in the agreed iPSP completed and included in the application?</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td></td>
</tr>
<tr>
<td><strong>If no, may be an RTF issue - contact DPMH for advice.</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>BPCA:</strong></td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td>Is this submission a complete response to a pediatric Written Request?</td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>Proprietary Name</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Is a proposed proprietary name submitted?</td>
<td>☑</td>
<td>☐</td>
<td>☐</td>
<td>Submitted on 8-2-16 under SDN 5</td>
</tr>
<tr>
<td><strong>If yes, ensure that the application is also coded with the supporting document category, “Proprietary Name/Request for Review.”</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>REMS</strong></td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>Comment</td>
</tr>
<tr>
<td>Is a REMS submitted?</td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td></td>
</tr>
<tr>
<td><strong>Prescription Labeling</strong></td>
<td>☑</td>
<td>Not applicable</td>
<td></td>
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<tr>
<td>Check all types of labeling submitted.</td>
<td>☑</td>
<td>Parking Insert (Prescribing Information)(PI)</td>
<td></td>
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</tr>
<tr>
<td>☑</td>
<td>Patient Package Insert (PPI)</td>
<td></td>
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<tr>
<td>☑</td>
<td>Instructions for Use (IFU)</td>
<td></td>
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<tr>
<td>☑</td>
<td>Medication Guide (MedGuide)</td>
<td></td>
<td></td>
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<tr>
<td>☑</td>
<td>Carton labeling</td>
<td></td>
<td></td>
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<tr>
<td>☑</td>
<td>Immediate container labels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>☑</td>
<td>Diluent labeling</td>
<td></td>
<td></td>
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<tr>
<td>☑</td>
<td>Other (specify)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is Electronic Content of Labeling (COL) submitted in SPL format?</td>
<td>☑</td>
<td>☐</td>
<td></td>
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</tr>
</tbody>
</table>

[http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm)

[http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm](http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm)

Version: 4/12/2016
If no, request applicant to submit SPL before the filing date.

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>4/12/2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the PI submitted in Physician Labeling Rule (PLR) format?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>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?</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For applications submitted on or after June 30, 2015:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLL) format?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>For applications submitted on or after June 30, 2015:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>If PI not submitted in PLL 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?</td>
<td></td>
<td></td>
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<tr>
<td>If no waiver or deferral, request applicant to submit labeling in PLL format before the filing date.</td>
<td></td>
<td></td>
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<tr>
<td>Has all labeling [PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (send WORD version if available)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?</td>
<td></td>
<td></td>
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<tr>
<td><strong>OTC Labeling</strong></td>
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<td>Not Applicable</td>
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<tr>
<td>Check all types of labeling submitted.</td>
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<tr>
<td>Outer carton label</td>
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<tr>
<td>Immediate container label</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blister card</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Blister backing label</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Consumer Information Leaflet (CIL)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Physician sample</td>
<td></td>
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<tr>
<td>Consumer sample</td>
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Reference ID: 3986410

Version: 4/12/2016
<table>
<thead>
<tr>
<th>Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>If yes, specify consult(s) and date(s) sent:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CDRH-Device: 7-12-16</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>CDRH-OC: 7-12-16</td>
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<tr>
<td>DPMH-PLL: 8-23-16</td>
<td></td>
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<tr>
<td>CBER/DVRPA: 8-23-16</td>
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<tr>
<td>OSI: 8-26-16</td>
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<tr>
<td>COA: 9-6-16</td>
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<tr>
<td>DMEPA-HF: 9-6-16</td>
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<table>
<thead>
<tr>
<th>End-of Phase 2 meeting(s)?</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Date(s):</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>5-21-14</td>
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<tr>
<td>5-8-14: CMC only</td>
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<table>
<thead>
<tr>
<th>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Date(s):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-16-15*</td>
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<table>
<thead>
<tr>
<th>Any Special Protocol Assessments (SPAs)?</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date(s):</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Meeting Minutes/SPAs</th>
<th>YES</th>
<th>NO</th>
<th>NA</th>
<th>Comment</th>
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</table>

| Reference ID: 3986410 | 4/12/2016 | 10 |
ATTACHMENT

MEMO OF FILING MEETING

DATE: 9/2/16

BACKGROUND:
DUPIXENT (dupilumab) injection is a human interleukin-4 and interleukin-13 antagonist indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical

Dupilumab was granted designation as a breakthrough therapy on 11-18-2014 under IND 107969.

REVIEW TEAM:

<table>
<thead>
<tr>
<th>Discipline/Organization</th>
<th>Names</th>
<th>Present at filing meeting? (Y or N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Project Management</td>
<td>RPM: Matthew White</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>CPMS/TL: Barbara Gould</td>
<td>N</td>
</tr>
<tr>
<td>Cross-Discipline Team Leader (CDTL)</td>
<td>Snezana Trajkovic</td>
<td>Y</td>
</tr>
<tr>
<td>Division Director/Deputy</td>
<td>Kendall Marcus/Jill Lindstrom</td>
<td>Y/Y</td>
</tr>
<tr>
<td>Office Director/Deputy</td>
<td>Julie Beitz/Amy Egan</td>
<td>Y/Y</td>
</tr>
<tr>
<td>Clinical</td>
<td>Reviewer: Brenda Carr</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Snezana Trajkovic</td>
<td>Y</td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td>Reviewer: Jie (Jack) Wang</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Yow-Ming Wang</td>
<td>Y</td>
</tr>
<tr>
<td>Pharmacometrics</td>
<td>Reviewer: Dhananjay Marathe</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Jeffry Florian</td>
<td>N</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>Reviewer: Carin Kim</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>TL: Mohamed Alish</td>
<td>Y</td>
</tr>
<tr>
<td>Nonclinical (Pharmacology/Toxicology)</td>
<td>Reviewer: Renqin Duan</td>
<td>Y</td>
</tr>
</tbody>
</table>

Reference ID: 3986410
### Product Quality (CMC) Review Team:

<table>
<thead>
<tr>
<th>Task</th>
<th>TL:</th>
<th>Y/N</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT:</td>
<td>Cristina Ausin</td>
<td>Y</td>
</tr>
<tr>
<td>RBPM:</td>
<td>Melinda Bauerlien</td>
<td>N</td>
</tr>
<tr>
<td>Drug Substance/Drug Product</td>
<td>Gunther Boekhoudt</td>
<td>Y</td>
</tr>
<tr>
<td>Microbiology - Drug Substance</td>
<td>Maria Jose Lopez-Barragan</td>
<td>N</td>
</tr>
<tr>
<td>Microbiology – Drug Product</td>
<td>Lakshmi Narasimhan</td>
<td>Y</td>
</tr>
<tr>
<td>Facility</td>
<td>Wayne Seifert</td>
<td>N</td>
</tr>
<tr>
<td>Labeling (BLAs only)</td>
<td>Jibril Abdus-Samad</td>
<td>N</td>
</tr>
<tr>
<td>OMP/OMPI/DMPP (MedGuide, PPI, IFU)</td>
<td>Sharon Mills</td>
<td>Y</td>
</tr>
<tr>
<td>OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)</td>
<td>Tara Turner</td>
<td>N</td>
</tr>
<tr>
<td>OSE/DMEPA (proprietary name, carton/container labeling)</td>
<td>Carlos Mena-Grillasca</td>
<td>Y</td>
</tr>
<tr>
<td>OSE/DRISK (REMS)</td>
<td>Robert Pratt</td>
<td>Y</td>
</tr>
<tr>
<td>Other reviewers/disciplines</td>
<td></td>
<td></td>
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<tr>
<td>CDRH/ DAGRID</td>
<td>Sapana Patel</td>
<td>Y</td>
</tr>
<tr>
<td>TL:</td>
<td>Alan Stevens</td>
<td>N</td>
</tr>
<tr>
<td>OSI</td>
<td>Roy Blay</td>
<td>N</td>
</tr>
<tr>
<td>TL:</td>
<td>Janice Pohlman</td>
<td>N</td>
</tr>
<tr>
<td>DPMH</td>
<td>Christos Mastroyannis</td>
<td>Y</td>
</tr>
<tr>
<td>TL:</td>
<td>Tamara Johnson</td>
<td>Y</td>
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<tr>
<td>OSE-DPV</td>
<td>Ida-Lina Diak</td>
<td>Y</td>
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<tr>
<td>OSE</td>
<td>Tri Bui-Nguyen</td>
<td>Y</td>
</tr>
<tr>
<td>DDDDP</td>
<td>Nancy Xu</td>
<td>Y</td>
</tr>
<tr>
<td>ODE III</td>
<td>Maria Walsh</td>
<td>Y</td>
</tr>
</tbody>
</table>

### FILING MEETING DISCUSSION:

**GENERAL**

- **505(b)(2) filing issues:**
  - Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?
    - ☒ Not Applicable
    - ☐ YES ☐ NO

Version: 4/12/2016
<table>
<thead>
<tr>
<th>Question</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Per reviewers, are all parts in English or English translation?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If no, explain:</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>• Electronic Submission comments</td>
<td>Not Applicable</td>
<td>No comments</td>
</tr>
<tr>
<td>List comments:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLINICAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td>Not Applicable</td>
<td>FILE</td>
</tr>
<tr>
<td>• Clinical study site(s) inspections(s) needed?</td>
<td></td>
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<tr>
<td>If no, explain:</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>• Advisory Committee Meeting needed?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments:</td>
<td>YES</td>
<td>Date if known: NO</td>
</tr>
<tr>
<td>If no, for an NME NDA or original BLA, include the reason. For example:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o this drug/biologic is not the first in its class</td>
<td></td>
<td></td>
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<tr>
<td>o the clinical study design was acceptable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o the application did not raise significant safety or efficacy issues</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o 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</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If the application is affected by the AIP, has the</td>
<td></td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>
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?

**Comments:**

<table>
<thead>
<tr>
<th>CONTROLLED SUBSTANCE STAFF</th>
<th></th>
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<tbody>
<tr>
<td>• Abuse Liability/Potential</td>
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**Comments:**

<table>
<thead>
<tr>
<th>CLINICAL MICROBIOLOGY</th>
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<tr>
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**Comments:**

<table>
<thead>
<tr>
<th>CLINICAL PHARMACOLOGY</th>
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</tr>
</thead>
<tbody>
<tr>
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</table>

**Comments:** Information requests to be included in the filing communication

<table>
<thead>
<tr>
<th>• Clinical pharmacology study site(s) inspections(s) needed?</th>
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<tbody>
<tr>
<td>✔ NO</td>
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**Comments:**

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<tr>
<th>BIOSTATISTICS</th>
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**Comments:** Information request to be included in the filing communication

<table>
<thead>
<tr>
<th>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</th>
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<tbody>
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**Comments:**

<table>
<thead>
<tr>
<th>PRODUCT QUALITY (CMC)</th>
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<tbody>
<tr>
<td>✔ Not Applicable</td>
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</tbody>
</table>

**Comments:**

**New Molecular Entity (NDAs only)**

|  ✔ Not Applicable     |  |

**Comments:**

**Review issues for 74-day letter**
- Is the product an NME?  □ YES  □ NO

**Environmental Assessment**

- Categorical exclusion for environmental assessment (EA) requested?  □ YES  □ NO
  
  If **no**, was a complete EA submitted?  □ YES  □ NO

**Comments:**

**Facility Inspection**

- Establishment(s) ready for inspection?  □ YES  □ NO

**Comments:**

**Facility/Microbiology Review (BLAs only)**

□ Not Applicable  □ FILE  □ REFUSE TO FILE

**Comments:**

**CMC Labeling Review (BLAs only)**

□ Review issues for 74-day letter

**Comments:**

**APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)**

□ N/A

- 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?  □ YES  □ NO

- If so, were the late submission components all submitted within 30 days?  □ YES  □ NO
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>What late submission components, if any, arrived after 30 days?</td>
<td>N/A</td>
</tr>
<tr>
<td>Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</td>
<td>☒ YES</td>
</tr>
<tr>
<td>Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</td>
<td>☒ YES</td>
</tr>
<tr>
<td>Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</td>
<td>☒ YES</td>
</tr>
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</table>
REGULATORY PROJECT MANAGEMENT

Signatory Authority: Dr. Julie Beitz

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 10-28-16

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be suitable for filing.

Review Issues:

☒ No review issues have been identified for the 74-day letter.
☐ Review issues have been identified for the 74-day letter.

Review Classification:

☐ Standard Review
☒ Priority Review

ACTION ITEMS

☐ Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).

☐ If RTF, notify everyone who already received a consult request, OSE PM, and RBPM

☐ 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.

☒ If priority review, notify applicant in writing by day 60 (see CST for choices)

☒ Send review issues/no review issues by day 74

☐ Conduct a PLR format labeling review and include labeling issues in the 74-day letter

☒ Update the PDUFA V DARRTS page (for applications in the Program)

☐ Other

Annual review of template by OND ADRAs completed: April 2016

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/s/

MATTHEW E WHITE
09/15/2016
Signed of behalf of Barbara Gould, Chief, Project Management Staff
Council Members:
Donna Griebel, OND/ODEIII/DGIEP
Gerald Dal Pan, OSE
John Jenkins, OND
Karen Mahoney, OND/ODEII/DMEP
Leonard Sacks, OMP
Robert Temple, CDER
Sandra Benton, Executive Secretary

Attendees:
Jane Liedtka, OND/ODEIII/DDDP
Jill Lindstrom, OND/ODEIII/DDDP
Diane Maloney, CBER
Kendall Marcus, OND/ODEIII/DDDP
Richard Moscicki, CDER
Rigoberto Roca, OND/ODEII/DAAAP
Arthur Simone, OND/ODEII/DAAAP
Matthew Sullivan OND/ODEII/DAAAP
Rose Tiernan, OMP
Douglas Throckmorton, CDER

Topic: To discuss the breakthrough therapy (BT) designation request for Regeneron Pharmaceuticals, IND 107969, Dupilumab for the treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy.

Discussion: DDDP agreed that this drug is intended to treat a serious condition. Background is attached.

This BT request was initially circulated through the Council by email for review. One Council member had questions regarding the two trials submitted to support the BT determination. Both phase 2 trials were placebo controlled comparisons and it was unclear how dupilumab compared to available therapy.

DDDJP stated that a majority of patients with atopic dermatitis can achieve clinical improvement and disease control with nonpharmacologic interventions (e.g., emollient use), conventional topical therapies (including corticosteroids and calcineurin inhibitors), and environmental and occupational modifications, when necessary. Phototherapy is recommended as a treatment for both acute and chronic AD in children and adults, after failure of the measures mentioned above. Phototherapy, however, involves multiple visits and there are long-term side effects. With corticosteroids, there is a rebound flare effect that can be worse than before corticosteroid treatment. Prednisone is approved for the treatment of atopic dermatitis, but current practice guidelines recommend against its use. Please see page 3 of the background document for the recommended treatment guidelines for the management of atopic dermatitis.

The adverse event of concern with dupilumab is cutaneous T-cell lymphoma (CTCL) reported in one patient on therapy in trial #1225, open label long term. Lymphoma is difficult to diagnosis in these patients. DDDP also noted that CTCL was seen in a placebo patient in the another trial,
1026, phase 2 sequential ascending dose trial. This patient may have had CTCL when entering the trial. For the patient on study drug, the event seen may regress once the patient is off study drug.

DDDP, however, notes that many of the adverse events seen (see page 5 of background) were mild to moderate. Dupilumab could be a safer alternative, avoiding the toxicity of corticosteroids.

The phase 3 trials, as with the phase 2 trials, are planned to compare to placebo. There will be two monotherapy trials and one adjunctive trial. The Council asked what the focus of the three trials was – efficacy or safety? The Council did not recommend replication of the monotherapy trial unless there is an important safety reason or other question that needs to be addressed. One monotherapy and one adjunctive trial could be enough to support approval.

The Council believed that the main basis for granting this BT request is the possible improved safety compared to available therapy. The Council agreed with the review division’s recommendation to grant the request.

**Recommendation:** The Council recommended granting the breakthrough therapy designation request from Regeneron Pharmaceuticals, IND 107969, Dupilumab for the treatment of moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy.
Non Responsive

Attachment: Background Documents

Draft: S Benton 11/20/2014
R/D: J Lindstrom 11/20/2014
     J Liedtka 11/20/2014
Final: S Benton 12/15/2014
CDER Medical Policy Council Brief
Breakthrough Therapy Designation
**DDDP**

*Nov 14, 2014*

<table>
<thead>
<tr>
<th><strong>Summary Box</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. IND Number <strong>107969</strong></td>
</tr>
<tr>
<td>2. Company name <strong>Regeneron Pharmaceuticals Inc.</strong></td>
</tr>
<tr>
<td>3. Drug name <strong>Dupilumab</strong></td>
</tr>
<tr>
<td>4. Indication <strong>moderate-to-severe atopic dermatitis in adult patients who are not adequately controlled with or are intolerant to topical prescription therapy</strong></td>
</tr>
<tr>
<td>5. Is the drug intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition? <strong>Yes, moderate to severe atopic dermatitis that is not adequately controlled with topical prescription therapy is a serious condition.</strong></td>
</tr>
<tr>
<td>6. Does the preliminary clinical evidence indicate that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints? <strong>Yes, preliminary results of phase 2 trials demonstrate substantial improvement over placebo in subjects who are not adequately controlled by prescription topical therapies. Other than prednisone (which is approved for treatment of atopic dermatitis but not recommended for this use per current clinical guidelines), there are no products approved for the proposed indication. There are various formulations of topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) that are approved for the treatment of atopic dermatitis.</strong></td>
</tr>
</tbody>
</table>

**Division: DDDP**
**Medical officer:** Jane Liedtka, MD
**Clinical Team Leader:** Jill Lindstrom, MD

1. **Brief description of the drug**
   Dupilumab (REGN668 / SAR231893) is a fully human monoclonal antibody that binds to the IL-4 receptor alpha subunit (IL-4Rα), a component of Type I and Type II IL-4 receptors as well as the IL-13 receptor system. By binding to IL-4Rα, dupilumab blocks signaling by both IL-4 and IL-13. Dupilumab as a targeted immunomodulatory agent, selectively inhibits the Type-2 helper T cell (Th2) pathway, and therefore, may potentially provide therapeutic benefit without the full spectrum of side effects typically associated with the use of broad immunosuppressants. This mechanism of action is different from those of conventional AD therapies.

2. **Brief description of the disease and intended population**
   Atopic dermatitis (AD) is a chronic, pruritic inflammatory dermatosis that affects up to 25% of children and 2% to 3% of adults. AD is often associated with elevated serum immunoglobulin IgE levels and a personal or family history of type I allergies, allergic rhinitis, and asthma.
AD is a complex disease with a genetic predisposition strongly influenced by innate and adaptive immune responses, as well as environmental factors, including allergen exposure, irritants, microbes, diet, stress, and air quality. In patients with AD with increased IgE levels, nonlesional AD is associated with a selective expansion of TH2 cells in a dermal perivascular distribution. Nonlesional AD skin lesions contain immune infiltrates that produce cytokines, such as IL-4 and IL-13, which contribute to a defective epidermal barrier. Barrier defects lead to penetration by epicutaneous allergens that encounter Langerhans cells in the epidermis and dermal Dendritic Cells in the dermis to activate TH2 and TH22 cells involved in acute disease onset. The sponsor proposes that blockade of cytokines IL-4 and IL-13 by dupilumab will result in improvement in the signs and symptoms of moderate to severe atopic dermatitis in subjects with an inadequate response to topical prescription therapy.

Table 1: Summary of cytokine effects on the epidermis in patients with Atopic Dermatitis

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<td>IL-4</td>
<td>Increases permeability</td>
</tr>
<tr>
<td>IL-13</td>
<td>Increases inflammation</td>
</tr>
</tbody>
</table>

Source: Leung

Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with nonpharmacologic interventions (eg, emollient use), conventional topical therapies (including corticosteroids and calcineurin inhibitors), and environmental and occupational modifications, when necessary. Phototherapy is recommended as a treatment for both acute and chronic AD in children and adults, after failure of the measures mentioned above. Systemic immunomodulatory agents are indicated and recommended for the subset of adult and pediatric patients in whom optimized topical regimens using emollients, topical anti-inflammatory therapies, adjunctive methods, and/or phototherapy do not adequately control the signs and symptoms of disease, and contact dermatitis has been considered. Data from routine clinical care suggest that more than 10% of all patients with AD receive systemic anti-inflammatory treatment.

In patients with moderate, and especially severe, AD, its clinical manifestations and significant psychological and sociological sequelae result in a condition that has substantial negative impact on day-to-day functioning. In patients with moderate to severe atopic dermatitis, lesions cover a large percentage of the body surface area (BSA), typically 50% and often higher. The sleep disturbance
that results from itching and scratching in AD affects not only the quality of life (QOL), but also patient’s cognitive function, behaviour, and their performance and productivity. Patients with severe AD had significantly more nights during which sleep was affected (162 per year). The ISOLATE study (2002 patients) reported that AD affects patient’s self-esteem, mood, self confidence, and ability to establish and manage relationships. Approximately half (51%) of the patients experienced depression or unhappiness caused by their condition.

3. **Endpoints used in the available clinical data, endpoints planned for later studies, and endpoints currently accepted by the review division in the therapeutic area**

In the phase 2 trials R668-AD-1117 (POC, 12 weeks Rx, 55 active subjects) and R668-AD-1021 (dose-ranging, 16 weeks Rx, 318 active subjects) the sponsors primary efficacy endpoint was the percent change of eczema area and severity index (EASI) score from baseline to week 12. Other endpoints included the proportion of subjects with investigator’s global assessment (IGA) 0 or 1 (DDDPS recommended primary efficacy endpoint for phase 3 trials), percent change in peak puritus numerical rating scale (NRS) and percent patients with EASI 50,75 and 90.

The division recommended primary efficacy endpoint of the proportion of subjects with IGA 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥ 2 points at week 16 has been agreed upon with the sponsor for the phase 3 pivotal trials. The proportion of patients achieving EASI-75 (≥75% reduction from baseline in EASI score at week 16) has been agreed upon with the sponsor for one of the phase 3 pivotal trials secondary endpoints. These endpoints are considered by the division to directly measure the clinical benefit of a drug for AD.

4. **Brief description of available therapies (if any)**

Atopic dermatitis is currently treated primarily with topical corticosteroids (TCS), but continuous long-term application of these agents is not recommended because of the risk of side effects, both on the skin (irreversible skin atrophy, striae, dyspigmentation, acneiform eruptions, etc.) and those related to systemic absorption (eg, growth retardation in children, hypothalamic-pituitary axis effects, etc.). Topical calcineurin inhibitors (tacrolimus and pimecrolimus) are labeled for second line use and are generally effective and safe as short-term treatment (efficacy generally similar to mid potency TCS and not as good as higher potency TCS), but long-term continuous administration is not indicated, particularly because of concerns regarding a theoretical increased risk of infections, lymphomas, and skin malignancies. Prednisone is approved for the treatment of atopic dermatitis, but current practice guidelines recommend against its use.


Prevailing literature suggests that cyclosporine, methotrexate (MTX), mycophenolate mofetil (MMF), and azathioprine (AZA) are used the most and are more efficacious in
treating AD, whereas other agents (leukotriene inhibitors, oral calcineurin inhibitors) have limited data. Biologic drugs are relatively new and the lack of available data prevents a recommendation for use in AD at this time. The management of AD with systemic corticosteroids, although used frequently and shown to temporarily suppress disease, should generally be avoided because of short- and long-term adverse effects and an overall unfavorable risk-benefit profile. Short courses of oral corticosteroids may lead to atopic flares.²

5. **Brief description of any drugs being studied for the same indication that received breakthrough therapy designation**

No drugs have received breakthrough designation for atopic dermatitis.

6. **Description of preliminary clinical evidence**

Efficacy
The sponsor has completed 2 phase 2 trials that support the preliminary efficacy and safety of dupilumab in adults with moderate to severe atopic dermatitis (inadequately treated or intolerant to TCS). The proof of concept trial, #1117 was a placebo controlled comparison of dupilumab 300mg q week (55 subjects) vs placebo (54 subjects) for 12 weeks. After 12 weeks, the IGA 0-1 proportion reached approximately 40% and the EASI-75 (the proportion showing a 75% improvement in EASI score) reached about 60%. In trial #1117, there were no deaths and only one of the serious adverse events occurred in the dupilumab arm (facial fracture). The most frequent TEAE by SOC from the dupilumab treatment group were Infections and Infestations (31 [56.4%] for dupilumab vs. 31 [57.4%] for placebo). The most frequent infection was nasopharyngitis (22 [40.0%] for dupilumab vs. 10 [18.5%] for placebo).

The dose-ranging trial, #1021 randomized 380 subjects to 5 doses of dupilmab (300mg q wk, 300mg q 2 wks, 300mg q 4 wks, 200mg q 2 wks and 100mg q 4 wks) vs placebo for 16 weeks. The following table displays the summary of efficacy results for the dose-ranging trial.

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=61</th>
<th>100mg q4w n=65</th>
<th>300mg q4w n=65</th>
<th>200mg q2w n=61</th>
<th>300mg q2w n=64</th>
<th>300mg qw n=63</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Pt with IGA 0-1</td>
<td>1.6</td>
<td>12.3</td>
<td>21.5</td>
<td>27.9</td>
<td>29.7</td>
<td>33.3</td>
</tr>
<tr>
<td>% Pt with EASI 75</td>
<td>11.5</td>
<td>29.2</td>
<td>49.2</td>
<td>55.7</td>
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<td>60.3</td>
</tr>
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Source: reviewer’s table

Results are consistent with those of trial #1117 and display a dose-response. The sponsor and the Agency have agreed on the doses (dupilumab 300mg q wk and 300mg q 2 wks) to be explored in the phase 3 trials (induction phase). The sponsor’s development plan for phase 3 includes two identical “monotherapy trials” (Trials 1334 and 1416) followed by a “maintenance trial” for responders (Trial 4 of 6

Reference ID: 3673197
a single Phase 3 trial of dupilumab used in combination with topical corticosteroids, and an open-label trial (Trial 1225).

Safety
No deaths have occurred in the development program to date. No significant differences in laboratory tests or EKG readings have been detected in studies thus far. Serious adverse events (SAEs) in the dupilumab arms in earlier trials have included ↑CPK (DDDП agreed with the sponsor that this was not likely drug-related but was associated with extreme exercise), and facial fracture. The treatment emergent adverse events (TEAEs) reported more frequently overall and more often in the dupilumab dosing groups than placebo groups across studies were “nasopharyngitis” and “headache”. Injection site reactions occurred in a relatively small number of dupilumab-treated patients (2 - 5.5% in dupilumab arms vs 0-1.9% in placebo), but appeared to be proportionally higher compared to placebo patients. They were generally mild to moderate, resolved within two weeks or less and did not require any intervention.

In the dose-ranging trial #1021, the percentage of patients with any AE was similar across the active (70-79%) and placebo (75%) arms and showed no dose relationship. There were 8 serious TEAEs in 7 dupilumab patients (2.2%) compared to 2 serious TEAEs in 2 placebo patients (3.3%).

Adverse events of concern noted in the development program so far include:

- 50 yo male with Cutaneous T Cell Lymphoma(CTCL) in trial #1225-open label long term, Skin bx-Nov 2013-c/w eczema, Received dupilumab May1, 2013 through Aug 21, 2014, Skin lesions worsening so repeat Skin bx-Aug 26,2014-c/w CTCL

Of note is that there has also been a case of CTCL in a placebo subject. This occurred in trial #1026 a phase 2 sequential ascending dose trial. The subject was diagnosed when she worsened after 8 weeks of therapy and was biopsied.

7. Division's recommendation and rationale
Recommendation: DDDD recommends that breakthrough status be granted because moderate to severe atopic dermatitis with inadequate response to topical prescription medications is a serious condition and preliminary clinical evidence indicates a substantial improvement over available therapy.

8. Division’s next steps and sponsor’s plan for future development
Atopic dermatitis is predominantly a disease of pediatric patients. DDDD has never approved a product for atopic dermatitis studied exclusively in adults. The timing of pediatric trials has been a topic of debate within DDDD and within the agency; an advisory committee (AC) meeting to discuss the timing of study of biologics in pediatric subjects with severe atopic dermatitis is planned for Feb 2015. DDDD discussed this issue with EMA, and plans to continue to work with our European colleagues to harmonize the approach to pediatric drug development for atopic dermatitis.
9. References


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/s/

SANDRA J BENTON
12/15/2014

KENDALL A MARCUS
12/15/2014

RIGOBERTO A ROCA
12/15/2014
1. **Brief description of the drug**

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9. References


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/s/

----------------------------------------------------
JANE E LIEDTKA
11/14/2014

JILL A LINDSTROM
11/17/2014