

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761033Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA # 761033
Product Name: Cinqar (reslizumab)

PMR/PMC Description: Develop and validate an assay that is sufficiently sensitive, selective, and specific to reliably detect product specific antibodies of the IgE isotype.

PMR/PMC Schedule Milestones:

Final Report Submission: December 2016

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

Anaphylaxis was a rare adverse event in reslizumab treated patients. Anaphylaxis can be diagnosed and treated without understanding the underlying etiology of the event. The assay will be used to test retrospective samples and so the study can be done post-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.”

To develop and validate a product specific anti-IgE assay.

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.

Bioanalytical assay development and validation.

Required

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

Continuation of Question 4

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

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

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

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

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

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

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

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

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

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

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

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

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

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

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # 761033

Product Name: Cinqar (reslizumab)

PMR/PMC Description: Use the anti-reslizumab IgE assay developed under PMR1 to test serum samples from patients who had treatment associated anaphylaxis.

PMR/PMC Schedule Milestones:

Final Report Submission:

March 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

Anaphylaxis was a rare adverse event in reslizumab treated patients. Anaphylaxis can be diagnosed and treated without understanding the underlying etiology of the event. The assay will be used to test retrospective samples and so the study can be done post-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.”

To test serum samples from patients who had treatment associated anaphylaxis.

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 PMR is to test samples from already completed clinical trials. The serum samples are from patients who had treatment associated anaphylaxis.

Required

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

Dosing trials
Continuation of Question 4

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

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

Agreed upon:

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

Other

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

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

NDA/BLA # 761033

Product Name: Cinqar (reslizumab)

PMR/PMC Description: Submit a qualification report demonstrating the suitability of the commercial anti-alpha gal ELISA from (b) (4) that was used to analyze the sera of the four treatment-related anaphylaxis patients.

PMR/PMC Schedule Milestones:

Final Report Submission:

April 2016

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 sponsor provided analytical data on the levels of anti-alpha-gal IgE in the sera of the four treatment-related anaphylaxis patients. The test used was a commercial anti-alpha gal ELISA from (b) (4). Alpha-gal is a sugar linkage found in reslizumab carbohydrate groups. IgE anti-alpha-gal antibodies have been associated with anaphylaxis with another biologic, cetuximab. Therefore, to better understand the etiology of the anaphylactic responses in reslizumab treated patients the sponsor evaluated samples for the presence of anti-alpha-gal IgE using a commercial test. The sponsor did not submit a suitable qualification report for the assay during the review cycle. Because anaphylaxis can be diagnosed and treated without understanding the etiology this can be a PMR.

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 sponsor provide analytical data very late in the BLA review cycle showing that the four reslizumab treated patients with treatment related anaphylaxis did not have anti-alpha-gal IgE in the sera. The sponsor did not submit as suitable qualification report for the the commercial anti-alpha gal ELISA from (b)(4) during the review cycle so it remains a PMC.

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.

Bioanalytical validation 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)

Neutralizing antibodies to therapeutic monoclonals are primarily associated with loss of efficacy, not safety. FDA recommends that all anti-drug antibody positive patients be screened for neutralizing antibodies to help understand the potential impact of anti-drug antibodies in a wider population. The sponsor did not develop a neutralizing antibody assay during product development. Therefore assay development is being requested as a PMC.

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

To develop and validate an assay to detect neutralizing anti-reslizumab antibodies.

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:

Bioanalytical assay development and validation.

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)

Neutralizing antibodies to therapeutic monoclonals are primarily associated with loss of efficacy, not safety. FDA recommends that all anti-drug antibody positive patients be screened for neutralizing antibodies to help understand the potential impact of anti-drug antibodies in a wider population. The sponsor did not develop a neutralizing antibody assay during product development. Therefore assay development is being requested as a PMC.

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

To test sera from confirmed anti-drug antibody positive asthmatic patients for the presence of anti-reslizumab neutralizing antibodies.

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 PMC is to test samples from already completed clinical trials. The serum samples are from confirmed anti-drug antibody positive asthmatic patients.

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)

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

NDA/BLA # BLA# 761033
Product Name: Cinqar (reslizumab)

PMC #1 Description: To implement a (b) (4)
 in the drug substance manufacturing process. The final study report will be submitted according to 21 CFR 601.12.

PMC Schedule Milestones:	Final Report Submission:	<u>May 2017</u>
	Other:	<hr/> <hr/>

PMC #2 Description: _____

PMC Schedule Milestones:	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	<hr/> <hr/>

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

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

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

(b) (4)

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

The goal of this study is to incorporate (b) (4)
the quality of reslizumab

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:

Implement (b) (4) in the drug substance manufacturing process.

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)

The sponsor needs more data to understand the manufacturing capability before tightening the endotoxin limits. This is appropriate for a PMC because the risk of microbial contamination of the product is low. There are bioburden limits for the relevant samples.

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

The current endotoxin (b) (4) limits for these samples are high. The sponsor should re-evaluate these limits after data from 30 batches are collected and tighten the limits based on manufacturing capability.

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:

Re-evaluate and tighten the (b) (4) endotoxin acceptance criteria for the (b) (4) samples after manufacturing 30 batches of reslizumab.

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)

The sponsor needs to establish and validate the hold times to ensure that the (b) (4) can be held without compromising the microbial quality of the product. This is appropriate for a PMC because the sponsor has committed to initially set the hold times based on historical data. The hold times will be validated concurrently under a QA-approved protocol. The acceptance criteria of the protocol were provided in the BLA and were adequate. Therefore, risk of microbial contamination of the product is low.

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

The (b) (4) hold time of these steps needs to be validated at scale with three runs from quality microbiology perspective.

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:

Establish a hold time limit for the (b) (4)
These hold times should be validated at scale to demonstrate that these (b) (4) can be held under proposed worst-case conditions without compromising the microbial quality of the product.

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)

The implementation of a more unique identity test for incoming bulk drug substance material at the drug product manufacturing site after approval is acceptable because the sponsor has established other control strategies (e.g. identity testing for release of drug product) that will prevent the release of misidentified product into the market. However, an identity test with better capacity to discriminate from other protein substances for incoming drug substance material would be more appropriate to better reflect good manufacturing practices.

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

To develop an identity test with better capacity to discriminate from other protein substances for incoming drug substance material would be more appropriate to better reflect good manufacturing practices.

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:

A description of the identity test method and method validation. The proposed specification should include acceptance criteria to discriminate reslizumab drug substance from other potential protein drug substance materials at the drug product manufacturing site.

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)

The implementation of a tighter fill volume criteria range after approval is acceptable because the sponsor has established an upper fill volume criterion. While the established criterion does exceed the current volume recommended by USP, it does provide enough control to minimize any concerns typically associated with excessive overfill. The current excess volume would not leave enough remaining product to suggest it would encourage product pooling by clinicians because this product is indicated for a limited subset of asthma patients and will require multiple vials to achieve intended dosage for most patients. While the current overfill upper limit does not pose a serious concern to require adjustment prior to approval, it should be adjusted to align the sponsor manufacturing with compendial recommendations.

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

Implement tighter fill volume.

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:

Conduct vial filling process studies to determine the capacity of their filling equipment to consistently fill vials to a fill volume in agreement with USP recommendations. Data to support consistency of fill volume after fill adjustment studies should also be generated.

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)

There is a qualified dye ingress CCI test method; however this method was qualified using comprised positive controls with relatively large breaches ((b) (4) μm in size). The capability of the method to detect smaller breach sizes ((b) (4) μm) that allow for microbial ingress was not demonstrated. Therefore, a CCI test with increased sensitivity is requested as a PMC.

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

The dye ingress CCI test method qualification was performed with positive controls containing a relatively large breach size ((b) (4) μm). The study should be repeated with controls containing smaller breach sizes (≤ (b) (4) μm) to demonstrate that the method is capable of detecting smaller breach sizes that could allow microbial ingress.

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:

Teva will repeat the dye ingress CCI study using reslizumab 10 mL/20 mm vial with controls containing smaller breach sizes (≤ (b) (4) μm) to demonstrate capability of the method to detect smaller breach sizes.

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)

A microbial retention validation study for (b) (4) was executed at (b) (4) C instead of (b) (4) C temperature. This study did not consider the effect of worst case or (b) (4) on the reslizumab product and the challenge organism. The microbial retention study will be repeated to include a (b) (4) range and mimic more closely production conditions. This is appropriate as a PMC because there is a theoretical concern that microorganisms may proliferate slightly more rapidly at the higher temperature.

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

The microbial retention validation study for (b) (4) was executed at (b) (4) C and the routine manufacturing temperature is (b) (4) °C. This study should be repeated to cover the temperature experienced during the (b) (4) process.

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:

Teva will repeat microbial retention study for (b) (4) to cover the temperature range experienced during the (b) (4) process.

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)

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

NDA/BLA # BLA# 761033
Product Name: Cinqar (reslizumab)

PMC #1 Description: To evaluate and revise, as needed, the acceptance criteria for all the drug substance and drug product release and stability specifications based on data from at least thirty released lots of reslizumab drug substance and drug product. The final study report(s) will be submitted according to 21 CFR 601.12.

PMC Schedule Milestones:	Final Report Submission:	<u>June 2019</u>
	Other:	_____

PMC #2 Description: _____

PMC Schedule Milestones:	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other:	_____

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

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

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

Assay acceptance criteria for several release and stability specifications, including but not limited to (b) (4) and potency; were set based on data from limited number of reslizumab batches. This is not an approvability issue because the validation results for these methods are adequate and the sponsor demonstrated that the process delivers a product of consistent quality. However, the Sponsor should re-evaluate and revise the acceptance criteria for these specifications as new data gets generated from sufficient number of reslizumab drug substance and drug product batches so the specifications better reflect commercial manufacturing experience.

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

The goal of this study is to evaluate additional data from sufficient number of reslizumab batches and revise accordingly the acceptance criteria for release and stability specifications for both drug substance and 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:

Teva should evaluate data from at least thirty lots, representing current commercial manufacturing process, to revise and update release and stability specification acceptance criteria for both drug substance and drug product.

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)

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

NDA/BLA # BLA# 761033
Product Name: Cinqar (reslizumab)

PMC #1 Description: To improve the overall control strategy of the drug substance
 manufacturing process (b) (4)

PMC Schedule Milestones:	Final Report Submission:	July 2017
	Other:	

PMC #2 Description: _____

PMC Schedule Milestones:	Final Report Submission:	MM/DD/YYYY
	Other:	

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

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

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

(b) (4)

This is not an approvability issue because the process validation results consistently demonstrated adequate control or clearance of both product- and process-related impurities to acceptable levels in reslizumab drug substance and drug product. However, the Sponsor should update the (b) (4) control strategy by including appropriate (b) (4) to offer a better control on overall process performance and improve the long term robustness of the process.

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

The goal of this study is further improve the overall (b) (4) control strategy for the reslizumab drug substance manufacturing process by including (b) (4)

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

Teva should improve their reslizumab control strategy by establishing appropriate (b) (4) throughout the reslizumab drug substance manufacturing process.

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)

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/s/

SALLY M SEYMOUR
03/22/2016

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

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

Memorandum

Date: March 1, 2016

To: Colette Jackson, Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

Subject: BLA # 761033 – CINQAIR[®] (reslizumab) injection, for intravenous
use

Reference is made to DPARP's consult request dated May 18, 2015, requesting review of the proposed Package Insert (PI), Patient Package Insert (PPI), and Carton/Container Labeling for CINQAIR[®] (reslizumab) injection, for intravenous use.

OPDP has reviewed the proposed PI entitled, "Reslizumab proposed-prescrib-info Feb 9 2016_BKS.docx" that was sent via email from DPARP to OPDP on February 16, 2016. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling entitled:

- "761033 Draft Carton Label - 100mg.pdf"
- "761033 Draft Container Label - 100mg.pdf"

that was sent from DPARP to OPDP on February 18, 2016. OPDP has no comments at this time on the proposed Carton/Container labeling.

Please note that comments on the proposed PPI were provided on February 29, 2016, under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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/s/

ADEWALE A ADELEYE
03/01/2016

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

PATIENT LABELING REVIEW

Date: February 26, 2016

To: Badrul Chowdhury, MD, PhD
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

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

Shawna Hutchins, MPH, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Aman Sarai, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, Pharm.D., MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): CINQAIR (reslizumab)

Dosage Form and Route: Injection for intravenous use

Application Type/Number: 761033

Applicant: Teva Pharmaceuticals

1 INTRODUCTION

On March 30, 2015 Teva Pharmaceuticals submitted for the Agency's review a Biologics License Application (BLA) for Reslizumab (CEP-38072). The submission also contained a request for a proprietary name review to obtain approval of the tradename CINQAIR. Reslizumab is intended to be administered as an intravenous (IV) infusion at a dose of 3mg/kg every 4 weeks with a proposed indication to reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on May 18, 2015 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), for CINQAIR (reslizumab) injection for intravenous use.

2 MATERIAL REVIEWED

- Draft CINQAIR (reslizumab) PPI received on January 4, 2016, and received by DMPP and OPDP on February 16, 2016.
- Draft CINQAIR (reslizumab) Prescribing Information (PI) received on January 4, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 16, 2016.
- Approved NUCALA (mepolizumab) comparator labeling dated November 4, 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 the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
02/26/2016

ADEWALE A ADELEYE
02/26/2016

SHAWNA L HUTCHINS
02/29/2016

LASHAWN M GRIFFITHS
02/29/2016



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

FINAL LABEL AND LABELING REVIEW

Date:	February 23, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad -S <small>Digitally signed by Jibril Abdus-samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S Date: 2016.02.23 14:39:53 -05'00'</small>
Through:	Tracy Denison, PhD, Quality Reviewer Division of Biotechnology Review and Research III Tracy A. Denison -S <small>Digitally signed by Tracy A. Denison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001154781, cn=Tracy A. Denison -S Date: 2016.02.23 14:47:13 -05'00'</small>
Application:	BLA 761033/0
Product:	Cinqair (reslizumab)
Applicant:	Teva Respiratory, LLC.
Submission Dates:	March 30 2015; January 4, 29; February 17 2016

Executive Summary:

The container label and carton labeling for Cinqair (reslizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 38/NF 33 December 1, 2015 and April 30, 2016]. Labeling deficiencies were identified and resolved. The container label and carton labeling submitted on February 17, 2016 is acceptable.

Background and Summary Description:

The Applicant submitted BLA 761033 Cinqair (reslizumab) on March 30 2015. Table 1 lists the proposed characteristics of Cinqair (reslizumab).

Table 1: Proposed Product Characteristics of Cinqair (reslizumab).

Proprietary Name:	Cinqair
Proper Name:	reslizumab
Indication:	reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids
Dose:	3 mg/kg via intravenous infusion over 20 to 50 minutes every 4 weeks
Route of Administration:	Intravenous infusion
Dosage Form:	injection
Strength and Container-Closure:	100 mg/10 mL single-dose vial
Storage and Handling:	Refrigerate at 2°C - 8°C (36°F - 46°F). Do not freeze. Protect the vials from light by storing in the original package until time of use.

Materials Reviewed:

Container Label submitted March 30, 2015

Carton Labeling submitted March 30, 2015

Start of Sponsor Material

Container Label



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

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

(1) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *does not conform*.

OBP Request: Relocate the dosage form "Injection" to appear below the proper name. For CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, Injection, can appear on the line below the proper name. *Applicant revised as requested.*

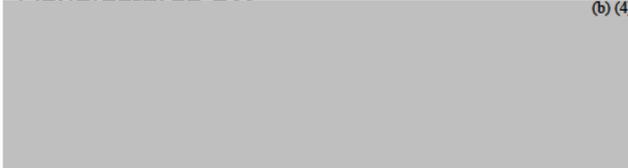
(2) The name, address, and license number of manufacturer; *does not conform*.

The Applicant/Licensee on the 356h form is the licensed manufacturer per 21 CFR 600.3(t). The Applicant must appear as "Manufactured by". Additionally, the U.S. License Number must appear with the manufacturer information per 21 CFR 610.61(b).

OBP Request: Revise the manufacturer information to appear as:

Manufactured by:

(b) (4)



On February 8, 2016 the Applicant submitted a change of applicant to Teva Respiratory, LLC and revised the manufacturer information to read:

Manufactured by:
Teva Respiratory, LLC.
Frazer PA 19355
U.S. License Number 2016

Acceptable.

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

(4) The expiration date; *conforms.*

(5) The recommended individual dose, for multiple dose containers; *not applicable. This is a single-dose product.*

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

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label. *Not applicable.*

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

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable.*

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

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *does not conform*.

OBP Request:

Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

On January 4, 2016, the Applicant noted there is approximately 5 mm the length of the vial to allow 'inspection of the contents'.

The Applicant's response is acceptable.

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

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.
However we recommend revising to active language.

OBP Request: Revise [REDACTED] (b) (4)" to "Dilute Prior to (b) (4)". *Applicant revised as requested.*

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

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

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

OBP Requests:

Delete or decrease the size of the graphic on the principal display panel (PDP), located above the proprietary name to increase the white space on the label to improve readability per 21 CFR 201.15. *Applicant revised as requested.*

Revise the strength presentation by including the strength per milliliter. Ensure the strength per total volume is more prominent than the strength per mL. For example:

100 mg/10 mL
(10 mg/mL)

Applicant revised as requested.

Revise "Single-Use Vial" to read "Single-Dose Vial". The Agency recommends consistent use of the appropriate package terms and discard statements. See the Agency's current thinking on this issue (FDA Draft Guidance: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple -Dose, Single-Dose, and Single-Patient-Use Containers for Human Use.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM468228.pdf>). *Applicant revised as requested.*

- G. 21 CFR 201.17 Drugs; location of expiration date; *conforms.*
- H. 21 CFR 201.25 Bar code; *conforms.*
- I. 21 CFR 201.50 Statement of identity; *conforms.*
- J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*
- K. 21 CFR 201.55 Statement of dosage; *does not conform.*

OBP Request: Add the statement "Usual Dosage: see insert" to comply with 21 CFR 201.55. *Applicant revised as requested.*

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

Start of Sponsor Material

Carton Labeling

(b) (4)



End of Sponsor Material

II. Carton

A. 21 CFR 610.61 Package Label:

- a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act] *does not conform.*

OBP Request: Relocate the dosage form "Injection" to appear below the proper name. For CDER-regulated biological products, the proper name should not include the finished dosage form. The finished dosage form, Injection, can appear on the line below the proper name. *Applicant revised as requested.*

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

The Applicant/Licensee on the 356h form is the licensed manufacturer per 21 CFR 600.3(t). The Applicant must appear as "Manufactured by". Additionally, the U.S. License Number must appear with the manufacturer information per 21 CFR 610.61(b).

OBP Request: Revise the manufacturer information to appear as:

Manufactured by:



On February 8, 2016 the Applicant submitted a change of applicant to Teva Respiratory, LLC and revised the manufacturer information to read:

Manufactured by:
Teva Respiratory, LLC.
Frazer PA 19355
U.S. License Number 2016

Acceptable.

c) The lot number or other lot identification; *conforms.*

d) The expiration date; *conforms.*

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *does not conform.*

OBP Request: Revise the statement "[redacted]" to read "Sterile. No preservative." To comply with 21 CFR 610.61(e). *Applicant revised as requested.*

f) The number of containers, if more than one; *not applicable.*

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

h) The recommended storage temperature; *conforms*.

i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *does not conform*. Include a warning not to shake.

OBP Request: Revise the storage statement to include "do not shake." For example: "Store in the refrigerator at 2°C - 8°C (36°F - 46°F) in original carton to protect from light. Do not freeze. Do not shake. *Applicant revised as requested*."

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

k) The route of administration recommended, or reference to such directions in an enclosed circular; *conforms*.

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

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

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

o) The adjuvant, if present; *not applicable*.

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

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

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *does not conform*.

OBP Request: Add the statement "No U.S. standard of potency" to comply with 21 CFR 610.61(r). *Applicant revised as requested.*

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

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

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

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

D. 21 CFR 610.64 Name and address of distributor; *does not conform*. *The licensed manufacturer/Applicant is not listed on the labeling. See manufacturer information request above.*

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

"Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated.

The Applicant revised as requested by listing only the Applicant.

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

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

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

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*. *However, we recommend revising to active language.*

OBP Request: Revise (b) (4) "Dilute Prior to (b) (4)". *Applicant revised as requested.*

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

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

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

OBP Requests:

Delete or decrease the size of the graphic on the PDP, located above the proprietary name to increase the white space on the label to improve readability per 21 CFR 201.15. *Applicant revised as requested.*

Revise the strength presentation by including the strength per milliliter. Ensure the strength per total volume is more prominent than the strength per mL. For example:

100 mg/10 mL

(10 mg/mL)

Applicant revised as requested.

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

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

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

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

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

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*. *However we recommend revising the list of ingredients to comply with USP General Chapters: <1091> Labeling of Inactive Ingredients.*

OBP Request: Revise the statement of ingredients to comply with with USP General Chapters: <1091> Labeling of Inactive Ingredients. For example:

Each mL contains 10 mg reslizumab, glacial acetic acid (0.12 mg), sodium acetate trihydrate (2.45 mg), and sucrose (70 mg).

Applicant revised as requested.

CDER Labeling Recommendations

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

A. Vial Container Label

1. Rotate the orientation of the text on the side panel so that it appears horizontally in the same direction as the information on the PDP to help ensure the safe use of this product.
2. Revise the storage statement to read "Store at 2°C - 8°C (36°F - 46°F) in original carton to protect from light. Do not freeze. Do not shake."

Conclusions:

The container label and carton labeling for Cinqair (reslizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), [USP 38/NF 33 December 1, 2015 and April 30, 2016]. Labeling deficiencies were identified and resolved. The container label and carton labeling submitted on February 17, 2016 is acceptable (see below).



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, Office of Drug
Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Memo

Date: December 30, 2015 **Consult Received:** October 8, 2015

From: Carol H. Kasten, MD, Medical Officer
Division of Pediatric and Maternal Health, Maternal Health Team
Office of Drug Evaluation IV (ODE IV)

Through: Tamara Johnson, MD, MS, Team Leader
Maternal Health Team
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health, ODE IV

To: Division of Pulmonology, Allergy and Rheumatology Products

Drug: Cinqair (reslizumab), BLA 761-033

Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Proposed Indication: to reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids

Subject: Labeling Review

Consult Request: “To comply with the Pregnancy and Lactation Labeling (PLLR), DPARP would like to request the Maternal Health Team to review Section 8.1 of the proposed label. DPARP will provide revised labeling for the Animal Data section.”

Documents Reviewed:

- Original BLA submission, annotated and draft labeling
- Nucala® (mepolizumab) labeling, revised November, 2015, BLA 125-526
- DPMH-MHT Review of mepolizumab, Miriam Dinatale, D.O. primary author, Dated June 8, 2015, DARRTS Reference ID: 3775784

INTRODUCTION

Teva Branded Pharmaceutical Products R&D, Inc. submitted BLA 761033 on March 30, 2015 for the new molecular entity (NME) reslizumab (tradename, Cinqair), a humanized monoclonal antibody (mAb) which binds to cytokine IL-5. The goal of treatment with reslizumab is to improve the lung function and reduce exacerbations of asthmatic patients with high blood concentrations of eosinophils. The Division of Pulmonology, Allergy and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH-MHT) on October 8, 2015, to review and provide labeling recommendations for the Pregnancy (8.1) and Lactation (8.2) subsections for reslizumab.

BACKGROUND

Asthma

Asthma is chronic inflammatory disorder characterized by acute symptoms of wheezing, shortness of breath and coughing.^{1,2} Patients may have exacerbations of their asthma that can require treatment with high doses of oral steroids, in addition to inhaled steroids and short-acting or long-acting β -agonists. Specific cytokines, including IL-5, are involved in mediating asthma symptoms and severity in some patients. IL-5 can mediate recruitment and activation of eosinophils, and mAbs targeted to bind to IL-5 have been found to reduce exacerbations in a subset of patients with ‘eosinophilic asthma (EA).’ EA is characterized by increased concentrations of eosinophils in sputum and blood and patients in the EA subset frequently have severe symptomatology and exacerbations.³

Adverse Outcomes of Asthma in Pregnancy

Asthma is one of the most frequent chronic conditions of pregnancy and is estimated to affect 3.7 to 8.4% of pregnant women.⁴ If it is poorly controlled, asthma is a risk factor for several serious adverse perinatal outcomes.^{5,6,7,8,9} Common adverse perinatal

¹ Akinbami L, Moorman J, *et al.* Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. NCHS data brief, no 94. Hyattsville, MD: National Center for Health Statistics. 2012.

² Garcia G, Taillé C, *et al.* Anti-interleukin-5 therapy in severe asthma. *Eur Respir Rev* 2013;22:251–257. DOI: 10.1183/09059180.00004013

³ Robinson D, Kariyawasam H. Mepolizumab for eosinophilic severe asthma: recent studies, *Expert Opinion on Biological Therapy*. 2015;15:909-914, DOI: 10.1517/14712598.2015.1041911. Link to this article: <http://dx.doi.org/10.1517/14712598.2015.1041911>

⁴ NAEPP Quick Report - Managing asthma during pregnancy: recommendations for pharmacologic treatment. *J Allergy Clin Immunol*;115:34-46.doi:10.1016/j.jaci.2005.10.023.

⁵ Murphy V, Schatz M. Asthma in pregnancy: a hit for two. *Eur Respir Rev* 2014;23:64–68. DOI: 10.1183/09059180.00008313.

⁶ Murphy V, Namazy J, *et al.* A meta-analysis of adverse perinatal outcomes in women with asthma. *BJOG* 2011; 118:1314–1323. 10.1111/j.1471-0528.2011.03055.x

⁷ Namazy J, Murphy V, *et al.* Effects of asthma severity, exacerbations and oral corticosteroids on perinatal outcomes. *Eur Respir J* 2013; 41: 1082–1090. DOI: 10.1183/09031936.00195111

outcomes include prematurity, low birth weight (LBW), small for gestational age (SGA) and preeclampsia. Women with moderate to severe asthma are at greatest risk for these adverse outcomes.^{10,11,12} The relative risk of premature delivery among women with asthma is estimated to be 1.41 (95% CI 1.23-1.62) compared to pregnant women without asthma. Relative risks for LBW and SGA are 1.46 (95% CI 1.22-1.75) and 1.22 (95% CI 1.14-1.31) respectively, for asthmatic vs. non-asthmatic pregnant women.¹³ Pregnant asthmatic women are half again (RR 1.54 (95% CI 1.32-1.81)) as likely to develop preeclampsia compared to pregnant women without asthma. Among pregnant asthmatic women, the greatest risk factor for delivery of a low birth weight baby is poorly controlled asthma. Women who have one or more exacerbations of their asthma while pregnant are three times more likely to deliver an LBW baby compared to asthmatic women without exacerbations (RR 3.02, (95% CI 1.87-4.89)).¹⁴ Although the data reviewed are not from randomized controlled clinical trials, based on the totality of the information available, there appears to be a clinically meaningful risk of adverse perinatal outcomes associated with poorly controlled asthma. Therefore, the clinical considerations section should include this information on the disease-associated maternal and fetal risk.

Medical Practice Organizations, NIH Recommendations for Asthma Management during Pregnancy

In 2000, the American College of Obstetricians and Gynecologists (ACOG) and the American College of Allergy, Asthma and Immunology (ACAAI) published a position statement on the risk of severe asthma during pregnancy.¹⁵ In 2004, the NIH-sponsored National Asthma Education and Prevention Program (NAEPP) Working Group on Asthma and Pregnancy stated that, “It is safer for pregnant women with asthma to be treated with asthma medications than to have asthma symptoms or exacerbations and reduced lung function that may potentially impair oxygenation for the fetus.”¹⁶ In 2008, ACOG published a Practice Bulletin on asthma in pregnancy echoing the NAEPP report and reiterated that premature delivery, preeclampsia, growth restriction and other

⁸ Triche E, Saftlas A, *et al.* Association of asthma diagnosis, severity, symptoms, and treatment with risk of preeclampsia. *Obstet Gynecol* 2004;104:585–93.

⁹ Tamasi L, Bohacs A, *et al.* Asthma in pregnancy – from immunology to clinical management. *Multidiscip Respir Med* 2010;5:259-263.

¹⁰ Wang G, Murphy V, *et al.* The risk of maternal and placental complications in pregnant women with asthma: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med, Early Online*: 1–9. 2013 Informa UK Ltd. DOI: 10.3109/14767058.2013.847080.

¹¹ See Murphy V, Schatz M, *et al.*

¹² See Murphy V, Namazy J, *et al.*

¹³ See Murphy V, Namazy J, *et al.*

¹⁴ Namazy J, Murphy V, *et al.*

¹⁵ American College of Allergy, Asthma and Immunology and the American College of Obstetricians and Gynecologists. Position Statement-The use of newer asthma and allergy medications during pregnancy. *Annals Allergy Asthma Immunology*. 2000;84:475-480.

¹⁶ National Asthma Education and Prevention Program. Working Group Report on managing asthma during pregnancy: recommendations for pharmacologic treatment. Update 2004. DHHS, NIH, NHLBI, NIH publication No. 05-5236. March 2005.

maternal and fetal morbidities could result from poorly controlled asthma.¹⁷ In 2014, ACOG reaffirmed their 2008 Practice Bulletin on asthma in pregnancy.¹⁸

Biologic Drug Product

Reslizumab is the second in a class of anti-IL-5 mAbs. The first anti-IL-5 mAb, mepolizumab, was approved on November 4, 2015.¹⁹ Reslizumab is a recombinant humanized mAb of the immunoglobulin-G4 kappa (IgG4/kappa) isotype produced in a mammalian cell expression system targeted to bind to IL-5. The proposed mechanism of action is that binding of reslizumab to IL-5 interferes with IL-5 signaling via its receptor to recruit, differentiate, and activate eosinophils. This is thought to reduce eosinophilic inflammation in the lungs of patients with asthma. *In vitro* assays have demonstrated that reslizumab binds to human IL-5 and blocks proliferation of an IL-5 sensitive cell line.²⁰ Reslizumab has a molecular weight of approximately 147 kDa and a half-life of 24 days.

Immunoglobulins, Monoclonal Antibodies and Pregnancy

Most currently available mAbs are IgG immunoglobulins and have a structure comparable to endogenous immunoglobulins.²¹ Animal studies of pregnancy suggest that mAbs are handled similarly to those transferred from the mother during normal gestation.^{22,23} Maternal IgG immunoglobulins cross into the fetal circulation via active transport using Fc receptors.²⁴ IgG is the primary immunoglobulin class that is transferred although all four subclasses are transferred.²⁵ Fc receptors start to be expressed in the placenta at the beginning of the second trimester and as the Fc receptor concentration increases, the quantity of IgG transferred increases.²⁶ The greatest transfer of IgG occurs in the last 4 weeks of gestation such that at delivery, the neonate's concentration of IgG1 may be higher than that of the mother's.²⁷

Monoclonal Antibodies and Lactation

IgG mAbs are large proteins (> 100,000 Daltons) which, due to their size, are less likely to be transferred into breast milk than smaller drugs (< 200 Da)²⁸ such as lithium

¹⁷ ACOG Practice Bulletin – clinical management guidelines for Obstetrician-Gynecologists. *Obstet Gynecol* 2008;111:457-464.

¹⁸ See ACOG Practice Bulletin, accessed December 6, 2015. <http://www.acog.org/Resources-And-Publications/Practice-Bulletins-List>

¹⁹ Nucala®, BLA 125-526, Approved November 4, 2015.

²⁰ Cinqair Labeling version October 8, 2015.

²¹ Hyrich K, Verstappen S. Biologic therapies and pregnancy: the story so far. *Rheumatology* 2014;53:1377-1385. doi:10.1093/rheumatology/ket409

²² See Hyrich K, version October 8, 2015.

²³ See Hyrich K, Verstappen S.

²⁴ Sarno M, Mancari R *et al.* Are monoclonal antibodies a safe treatment for cancer during pregnancy? *Immunotherapy* (2013) 5(7), 733–741. 10.2217/IMT.13.64

²⁵ Firan M, Bawdon R, *et al.* The MHC class I-related receptor FcRn plays an essential role in the maternofetal transfer of globulin in humans. *Internat Immunol* 2001;13:993-1002.

²⁶ Palmeira P, Quinello C, *et al.* IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol* 2012;2012:985646.

²⁷ See Palmeira P, *et al.*

²⁸ Saji F, Samejima Y *et al.* Dynamics of immunoglobulins at the feto–maternal interface. *Rev of Reproduc.* 1999; 4: 81–89.

²⁹ Hale's 2012 Medications and Mother's Milk. 15th Edition, Amarillo, TX

carbonate (73.89 Da).^{29,30} Reslizumab has a molecular weight of 147,000 Da which reduces its ability to be transferred to into breast milk; however, there is at least a hypothetical risk that reslizumab may be transferred into breast milk. If present, reslizumab would likely undergo proteolysis in the breastfed infant's gastrointestinal tract. However, the local effects on the gastrointestinal tract and the potential for systemic exposure to reslizumab are unknown.^{31,32}

PLLR

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,"³³ also known as the Pregnancy and Lactation Labeling Rule (PLLR). 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 creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule³⁴ format to include information about the risks and benefits of using these products during pregnancy and lactation.

DISCUSSION

Nonclinical Information

Data from studies in mice and rabbits demonstrated no embryo-fetal toxicity from prenatal exposure to reslizumab at exposures up to 17 times greater than that measured in patients treated at the maximum recommended human dose. No congenital malformations were reported and mice exposed prenatally to reslizumab and followed for up to four months of age demonstrated no abnormalities. Similar results, (no embryo-fetal toxicity or congenital malformations observed) were reported for mepolizumab which had animal reproduction studies completed in cynomolgus monkeys, not mice and rabbits. For a more detailed discussion of the nonclinical studies, the reader is referred to the pharmacology toxicology review.

Reslizumab and Pregnancy

A search of the published literature in PubMed with the search terms 'reslizumab or Cinqair' and 'pregnancy' or 'pregnant' produced no references. A search of the toxicology databases (Reprotox, TERIS, Shepard's) found no listing, as would be expected with a drug not yet approved. The applicant did not conduct any studies on the

²⁹ See Hale's.

³⁰ Eskalith® (lithium carbonate), NDA 16-860, labeling revised March, 2004.

³¹ See Hale's.

³² LACTMED® The LactMed database is a National Library of Medicine database with information on drugs and lactation geared toward healthcare practitioners and nursing women.

³³ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

³⁴ *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).

use of reslizumab in pregnant women. Therefore, there are no human exposure data to identify a risk associated with prenatal reslizumab exposure. The mepolizumab labeling for pregnancy states that there were insufficient data from clinical trials to determine a drug associated risk for prenatal exposure to mepolizumab. The mepolizumab labeling contains no human data.

Analyses of the body of data on asthma in pregnancy and formal recommendations by nationally recognized medical practice organizations form the basis of the DPMH-MHT labeling recommendation to include a statement about the risk of poorly or inadequately treated maternal asthma under *(8.1) Pregnancy – Clinical Considerations, Disease-Associated Maternal and Fetal Risk*.

Reslizumab and Lactation

There were no publications found in PubMed using the search terms reslizumab and lactation, breastfeeding or breastfed. A search of the LactMed³⁵ database for information on reslizumab yielded no information, as would be expected for a NME. The applicant did not conduct a lactation study which would provide data for an assessment of exposure risk in breastfed infants of reslizumab treated lactating mothers. There is a hypothetical risk that reslizumab may be present in human milk and the drug may possibly be absorbed from the infant's gastrointestinal tract producing systemic exposure to reslizumab in the breastfed infant. However, the risk of this exposure is not known.

The mepolizumab lactation labeling contains no data on the presence or absence of mepolizumab in human breast milk and provides no information on IgG MAbs exposure via breastfeeding.

CONCLUSIONS

- There are no data on reslizumab use during pregnancy which could be used to assess the risk of prenatal exposure. Animal reproduction studies demonstrated no embryo-fetal toxicity from reslizumab administration during pregnancy.
- Pregnant women with poorly or inadequately treated asthma are at risk of adverse outcomes for themselves and their fetus.
- There are no data on reslizumab use during lactation which could be used to assess the exposure risk to a breastfed infant.

RECOMMENDATIONS

The following are the DPMH Maternal Health Team recommendations for the proposed labeling for CINQAIR in PLR format. DPMH-MHT revised subsections 8.1 and 8.2 in the CINQAIR labeling for compliance with PLLR. DPMH-MHT recommendations are below and will be presented on December 14, 2015. DPMH-MHT refers to the final BLA 761-033 action for final labeling.

³⁵ <http://toxnet.nlm.nih.gov/cgi-bin/sis/search2>

HIGHLIGHTS

CINQAIR[®] (reslizumab) Injection, for intravenous use
Initial U.S. Approval: 20XX

HIGHLIGHTS

INDICATIONS AND USAGE

(b) (4)

FULL PRESCRIBING INFORMATION: CONTENTS*

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

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

Clinical Considerations

Disease-Associated Maternal and Fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data

In two separate embryo-fetal development studies, mice and rabbits received (b) (4)

(b) (4)
Reslizumab was not teratogenic in mice or rabbits. Embryo-fetal development of IL-5 deficient mice has been reported to be general unaffected relative to wild-type mice.

In a prenatal and postnatal development study, pregnant CD-1 mice received reslizumab on gestation days 6 and 18 and on post-natal day 14 at (b) (4)

(b) (4)
Reslizumab did not have any effects on fetal development up to approximately 4 months after birth. Reslizumab crossed the placenta of pregnant mice

(b) (4) Serum concentrations in (b) (4) pups were approximately 6-8% of those in the dams (parental female mice), (b) (4)

8.2 Lactation

Risk Summary

It is not known whether reslizumab is present in human milk, the effects of reslizumab on the breast fed infant, or the effects of CINQAIR on milk production. However, human IgG is known to be present in human milk. Reslizumab is present in the milk of lactating mice following dosing during pregnancy [see *Use in Specific Populations (8.1)*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CINQAIR and any potential adverse effects on the breast-fed child from CINQAIR or 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/

CAROL H KASTEN
12/30/2015

TAMARA N JOHNSON
12/31/2015

LYNNE P YAO
01/04/2016



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

Office of Biotechnology Products
Division of Therapeutic Proteins
Rockville, MD 20852
Tel. 301-827-1709

Immunogenicity Memorandum

Date: 12/18/2015

From: João A. Pedras-Vasconcelos

Joao A. Pedras Vasconcelos -A
Digitally signed by Joao A. Pedras Vasconcelos -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2006005544
cn=Joao A. Pedras Vasconcelos -A
Date: 2015.12.18 11:45:39 -05'00'

Through: Amy Rosemberg, Team Leader

Amy S. Rosenberg -A
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ou=People, 0.9.2342.19200300.100.1.1=1300045963,
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Through: Susan Kirshner, Review Chief

Susan L. Kirshner -A
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0.9.2342.19200300.100.1.1=1300194629,
cn=Susan L. Kirshner -A
Date: 2015.12.18 12:32:36 -05'00'

Subject: BLA 761033 Cinqair (reslizumab) immunogenicity review

PRODUCT: Cinqair© (reslizumab)

OBP SYSTEMATIC NAME: MAB HUMANIZED (IGG4) (b) (4)
(IL5_HUMAN) [CEP38072]

INDICATION: Reslizumab is being developed for the treatment of ashma with a strong eosinophilic component.

ROUTE OF ADMIN. i.v.

DOSE REGIMEN: 3mg/kg every four weeks

APPLICANT: Teva Pharmaceuticals

CLINICAL DIVISION: DPARP

BLA stamp date: 03/29/2015

Primary Review due date: 12/16/15

PDUFA Action Date 03/28/2015

Summary and Recommendation:

Reslizumab is a humanized IgG4 monoclonal antibody. Therapeutic administration of the biologic product induces treatment-emergent anti-drug antibodies (ADA) in clinical studies. Subjects were classified as having a treatment-emergent ADA response if a sample tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample. Immunogenicity rates were determined using validated screening,

confirmatory, and titering assays. Data obtained from pivotal studies, which include patients enrolled in placebo controlled studies C38072/3081, 3082, 3083, and 3084 dosed with 3.0 mg/kg of reslizumab, showed that 53/983 patients (5.4%) developed treatment-emergent ADA with titers ranging from 1:1 to 1:106. Twenty-seven of 53 (51%) of these patients had transient responses. Transient responses were defined by the sponsor as those that are positive at a single time point and remained negative in the last study sample. In the long-term, open-label study, C38072/3085, using the 3.0 mg/kg dose, 49/1014 patients (4.8%) developed ADA with titers ranging from 1:2 to 1:33. ADA were transient in 20 patients (41%). The incidence of hypersensitivity reactions during drug infusion of reslizumab treated patients (30%) was similar to that seen in placebo-treated patients (39%). The basis for such hypersensitivity reactions is not known. However, hypersensitivity reactions have been reported to be more common in patients with asthma than in the general population¹. Overall, the reported rate of adverse events of all grades for phase 3 studies was similar between the ADA positive (65%) and ADA negative (67%) patients. Teva did not provide information on neutralizing antibodies, as the assay is currently under development. However there appears to be no association between the presence of anti-drug antibodies and either loss of efficacy or increased levels of adverse events.

The applicant reported six anaphylactic reactions in the asthma clinical program. Of these, four cases had a temporal link to infusion of 3mg/kg of reslizumab. These were observed in four female patients, two from study C3802/3083, one from study 3082 and one from study 3084. The four patients with treatment –related anaphylaxis tested anti-drug-IgG negative, but were not tested for product specific IgE. A product-specific IgE ELISA is currently under development by the applicant. There was also one placebo patient from study 3083 that suffered an episode of anaphylaxis. Two of the patients had medical histories of hypersensitivity/anaphylaxis to multiple allergens; the third had a history of drug sensitivities. The fourth was an adjudicated case and the predisposing factors are still unclear. Based on these histories the anaphylactic patients may have a predisposition to hypersensitivity reactions. The applicant reports no other drug-related anaphylaxis in the long-term extension study at the 3.0 mg/kg-dose.

Product-related factors in reslizumab may impact immunogenicity and affect the incidence of anaphylaxis. These factors include glycosylation, and residual nucleic acids and host cell proteins from the cell substrate used to manufacture reslizumab. The product is produced in the NSO murine cell line, and this cell line is known to introduce the carbohydrate sequence galactose-alpha1, 3-galactose (alpha-gal) into the carbohydrate side-chains of the monoclonal antibody during the glycosylation process. Glycoproteins with the alpha-gal carbohydrate sequence are commonly produced by most mammals but not by Old World monkeys, apes, and humans due to lack of expression of the enzyme α -1, 3-galactosyl transferase (α -1, 3GT) that is responsible for the addition of

¹ Gonzalez-Perez et al, Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review; *J Allergy Clin Immunol.* 2010 125:1098-1104

alpha-gal to glycoproteins. As a result, alpha-gal containing glycoproteins are highly immunogenic in humans, with as much as 1% of natural antibodies in sera, primarily IgG and IgM, being specific for this carbohydrate. This is in part due to exposure to gut flora which have the ability to add alpha-gal to their glycoprotein and glycolipid molecules, and in part through dietary exposure. While the majority of the human population has anti-alpha-gal IgG antibodies in their sera, a proportion of the population develops IgE antibodies specific for alpha-gal, and these antibodies are associated with allergies to meat products, and tick bites. IgE to alpha-gal has also been implicated in anaphylactic responses in colorectal cancer patients treated with cetuximab, an anti-Epidermal Growth Factor Receptor monoclonal antibody. Cetuximab is produced in Sp2/02 murine hybridoma cells, which also glycosylate proteins with alpha-gal-containing carbohydrates. The prevalence of hypersensitivity to cetuximab had a regional distribution strongest in southeastern United States and was associated with pre-existing IgE antibodies to alpha-gal. Three out of the four reslizumab-associated anaphylaxis cases occurred in geographical areas where tick allergies are known to arise. Although the patients tested negative for ADA in the screening assay, the available immunogenicity assays have a reported sensitivity of around 22 ng/ml, which is too high to reliably detect antigen specific serum IgE. Levels of antigen-specific IgE in sera are typically present in the low nanogram to high picogram per ml range. Recently the applicant had the sera of the four anaphylactic patients evaluated for anti-alpha gal IgE antibodies and reported negative findings. This information is still under review by the Agency and will be address in an addendum to the current report. Currently, the possibility that the anaphylactic responses were triggered by pre-existing sensitivities to alpha-gal remains an open question. Of note, mepolizumab, a recently approved humanized IgG1 produced in CHO cells, also specific for IL-5 and used to treat similar patient population of asthmatics had no reported cases of anaphylaxis. CHO cells are of Chinese Hamster origin but lack or are deficient in the α -1,3GT enzyme responsible for α -gal glycosylation of proteins. This suggests that in addition to factors intrinsic to the study population, product specific factors are likely playing a role in the reslizumab-associated anaphylactic events

Besides product glycosylation, residual NS/O derived host cell proteins and nucleic acids may also enhance product immunogenicity by potentially acting as adjuvants, or by stimulating pre-existing cross-reactive IgE responses to mouse proteins resulting in anaphylaxis. An impact of host cell derived impurities in the immunogenicity of a biologic was shown for Omnitrope where high concentrations of host cell proteins were associated with increased immunogenicity rates. Omnitrope is a recombinant human growth hormone commercialized in Europe and in the United States. Once additional purification steps were added to the manufacturing process to reduce the level of residual host cell impurities, the immunogenicity rates in subsequent clinical studies were reduced for this product.

The contribution of host cell-derived impurities to reslizumab anaphylaxis is unclear at this time. The residual host cell proteins and nucleic acids and alpha-gal levels measured by the applicant in reslizumab clinical lots are consistent for the lots used across the pivotal clinical studies. Residual host cell proteins and nucleic acids levels are within the

range expected for products produced in murine cell lines. Currently there are eight licensed monoclonal antibodies manufactured in NS/0 cells and five monoclonals produced in Sp2/0, and all but one, have a reported incidence of anaphylaxis. However, there are seven other approved monoclonal antibodies produced in CHO cells that also have reported cases of anaphylaxis, albeit at lower incidence rates, despite CHO cells typically not expressing the α -1, 3GT enzyme responsible for the addition of alpha-gal during glycosylation². Thus monoclonal antibody-triggered anaphylaxis is not restricted to products produced in murine cell lines.

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In summary, there are product-specific and patient-specific factors that could be contributing to the anaphylaxis events observed in the phase 3 clinical studies in eosinophilic asthma patients. The applicant did not adequately investigate the root causes of the anaphylactic events. Therefore, the product safety profile is not well understood at this time. I recommend approval of the product with a black box warning on the label concerning the higher risk of anaphylaxis and muscle toxicity, and a post-marketing requirement for the sponsor to develop a product specific anti-IgE ELISA to test the sera of past and future anaphylactic patients.

Introduction

Cinqair[®] (reslizumab) is a humanized IgG4 κ antibody that binds to human interleukin-5 (IL-5). IL-5 plays an important role in the differentiation, maturation, recruitment and

activation of human eosinophils. The mechanism of action for reslizumab includes its specific binding to IL-5, thereby preventing IL-5 binding to its cell-surface receptor on target cells. The exact epitope recognized by reslizumab on IL-5 was not revealed in the submission. IL-5 receptor is primarily found on the surface of cells involved in the etiology of asthma such as eosinophils, basophils, mast cells, and airway smooth muscle cells. Reslizumab is produced by recombinant DNA technology in murine myeloma Non-Secreting 0 (NS0) cells and is purified from the culture supernatant. Reslizumab is a glycoprotein with an approximate a molecular weight of 147 kDa. Cinqair[®] (reslizumab) injection is supplied as a sterile, single-use, preservative-free solution for intravenous infusion. Cinqair[®] (reslizumab) is supplied as 100 mg in a 10 mL glass vial. Each single-use vial contains 10 mg/mL reslizumab in an aqueous solution with a pH of 5.5 and 2.45 mg/mL sodium acetate trihydrate, 0.12 mg/mL glacial acetic acid as buffering agents and 70 mg/mL sucrose as a protein stabilizing agent.

Reslizumab is proposed as a treatment to reduce asthma exacerbations, relieve symptoms, and improve lung function in patients older than 12 years of age, with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids (ICS). The proposed dosing scheme is 3 mg/kg intravenously administered every 4 weeks. Efficacy for this indication is supported by two pivotal 16 week lung function studies (studies 3081 and 3084) and two pivotal 52 week exacerbation studies (3082 and 3083). There was also an open label study of 104 weeks in duration.

Immunogenicity Risk Assessment:

The product is a humanized IgG4 monoclonal antibody, and typically humanized monoclonals would be considered lower risk for immunogenicity as the appearance of neutralizing antibodies would primarily impact efficacy rather than safety. There are no known endogenous counterparts to this anti-IL-5 mAb and so little concern that immunogenicity would disrupt an extant regulatory pathway for IL-5 mediated activity. The principal issue of concern for this product regards the fact that the product is produced in a murine cell line (NSO), which is capable of adding xenogeneic carbohydrates like galactose- α 1, 3-galactose (alpha-gal) and N-glycolneuraminic acid (NGNA). Such xenogeneic glycans may not only increase immunogenicity rates, but have resulted in serious adverse events in with anaphylaxis, a life threatening condition being most severe. The severe asthmatic target patient population is also at higher risk of developing hypersensitivity responses⁴. During the pivotal clinical trials for reslizumab, two safety signals were observed. These safety signals were the higher levels of anaphylactic reactions and muscle toxicity observed in reslizumab-treated compared to placebo-treated patients. The presence of safety signals raises the risk of the product and should lead to a black box warning on the label, as well as specific immunogenicity related post-marketing requirements (see PMR/PMC section at the end of the review).

Immunogenicity Assays

⁴ Gonzalez-Perez et al, Anaphylaxis epidemiology in patients with and patients without asthma: a United Kingdom database review; *J Allergy Clin Immunol*. 2010 125:1098-1104

Reslizumab had a complex development history. Reslizumab was first developed by Schering Plough, then Cephalon ^{(b) (4)} and lastly Teva who sponsored the BLA and was responsible for the completing the phase 3 studies used to support the application. As a result, different screening antibody assays were developed by each company, as summarized in the table below.

Table 5: Binding Assays Used to Determine Reslizumab Anti-Drug Antibodies

Sponsor	Binding ADA method			
	Format	Positive Control	Screen cut point	Confirmatory cut point
Schering Plough	^{(b) (4)}			
Cephalon ^{(b) (4)}				
Teva				

ADA = anti-drug antibody; RU = response units; ELISA = enzyme-linked immunosorbent assay; OD = optical density

Teva's anti-drug antibody assay went through three different procedures, each representing an improvement over previous versions, culminating in the current SOP-015162. A summary of the key parameters of these assays is provided below.

Table 6: Summary of Key Parameters of Reslizumab Anti-Drug Antibody Methods

Parameter	SOP-014745 (Phase 1 study C38072/1102 in healthy subjects)	SOP-015084 (Phase 1 study C38072/1107 in healthy subjects)	SOP-015162 (Phase 3 studies 3081, 3082, 3083, 3084, and 3085 in asthma patients)
Minimum Required Dilution	^{(b) (4)}		
Relative sensitivity (ng/mL)			
Drug tolerance (µg/mL)			

^{(b) (4)}

PC = positive control

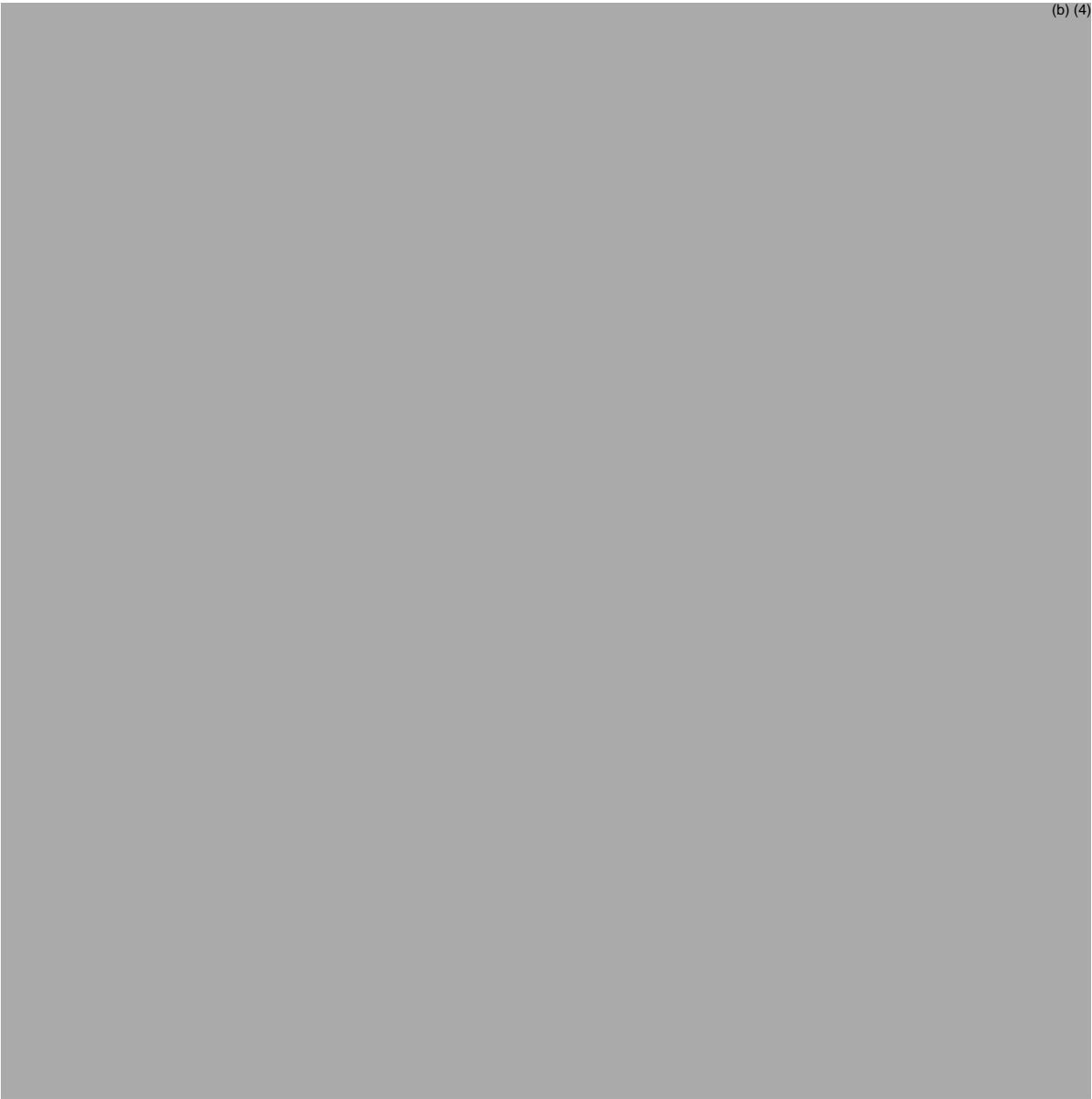
In section 5.3.1.4 of the BLA Teva included the analytical reports for all the various SOPs used for the anti-drug antibody assay. The current review will concentrate on the validation of the assay used to test the pivotal phase 3 studies.

Reviewer comment:

The applicant followed an incomplete step-wise approach to examining product immunogenicity. The applicant developed screening, confirmatory and titering assays. Samples testing positive in the screening and confirmatory assays are considered treatment-emergent anti-drug antibody positive. These samples are also tested using the

titering assay. According to FDA recommendations in the Draft Guidance for Industry Assay Development for Immunogenicity Testing of Therapeutic Proteins, 2009, samples that confirm positive should be assessed for their ability to neutralize drug activity. However, the applicant did not submit any information on a neutralizing antibody assay. Following the late cycle meeting on 11/23/2015 the applicant agreed to develop a neutralizing antibody assay and to test confirmed treatment emergent samples using this assay. This can be handled post-marketing, as there is no association between anti-drug antibody status and altered PK/PD, or serious adverse events (see later clinical results section). Draft language for the neutralizing ab assay can be found at the end of the report.

Method Validation Report: SOP-015162-AVR-01: Validation of a bridging ELISA for the analysis of anti-reslizumab antibodies in human serum.



12 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Assay assessment:

The information provided on the screening, confirmatory and titering assays indicate that the assays are suitable for their intended purpose. The applicant is currently developing the neutralizing antibody assay, and this will be a PMC because there was no observable association between ADA status and either safety and/or efficacy (see PMR/PMC section at the end of report).

The applicant is also developing a product-specific IgE ELISA as a result of anaphylaxis adverse events that were observed during the pivotal asthma clinical trials, and this will be a PMR because of its potential association with safety (see PMR/PMC section at the end of report).

Clinical Immunogenicity Results for Reslizumab Pivotal Studies:

The table below provides a summary of the pivotal clinical studies used for to support efficacy for reslizumab.

Pivotal efficacy studies: Phase (P) 3, randomized (R), double-blind (DB), placebo-controlled (PC) parallel-group (PG)

<i>Trial</i>	<i>Population by Eosinophil levels</i>	<i>N</i>	<i>Design</i>	<i>Dose mg/kg (IV q4wks)</i>	<i>Duration (Wks)</i>	<i>Endpoint</i>
3081	<i>Eos ≥ 400</i>	311	<i>P3 R DB PC PG</i>	<i>0.3 or 3</i>	16	<i>FEV1</i>
3082	<i>Eos ≥ 400</i>	488	<i>P3 R DB PC PG</i>	3	52	<i>Exacerbation</i>
3083	<i>Eos ≥ 400</i>	464	<i>P3 R DB PC PG</i>	3	52	<i>Exacerbation</i>
3084	<i>Any Eos</i>	492	<i>P3 R DB PC PG</i>	3	16	<i>FEV1</i>
3085	<i>Eos ≥ 400</i>	1008	<i>P3 OLE</i>	3	104	<i>Safety</i>

Table prepared by clinical reviewer

The immunogenicity information for each of the above studies was provided in individual immunogenicity study reports submitted in section 5.3.1.4. The table below summarizes the results for each study, along with the pooled immunogenicity results for proposed 3 mg dose.

Phase 3 immunogenicity results summary

Trial	Duration (Wks)	Dose mg/kg (IV q4wks)	N	ADA+ (%)	Sampling (Wks)	Transient (%ADA+)	Titers
3081	16	0.3 3	102 103	9 (8.7) 11 (10.6)	0, 8, 16 Same	7 (58) 9 (82)	1:2 to 1:45
3082	52	3	245	8 (3.3)	0, 16, 32, 48, 52	5 (63)	1:2 to 1:15
3083	52	3	226	15 (6.6)	0, 16, 32, 48, 52	3 (20)	1:2 to 1:106
3084	16	3	409	19 (3.9)	0, 8, 16	10 (53)	1:1 to 1:61
Pooled	NA	3	983	53 (5.4)	NA	27 (51)	1:1 to 1:106
3085 (extension)	104	3	1014	49 (4.8)	24, 48, 72, 96, and 4wks after last infusion	20 (41)	1:2 to 1:33

Table prepared by immunogenicity reviewer from individual study reports. NA not applicable

The following immunogenicity discussion was adapted from product and immunogenicity section of the AC briefing document prepared by this reviewer.

Subjects were classified as having a treatment-emergent ADA response if a sample tested positive in the assay at any of the postdose time points but not at the predose time point, or postdose ADA titer increased 4-fold or greater from a positive baseline ADA sample. Data obtained from the pivotal Phase 3 studies, which includes placebo controlled studies C38072/3081, 3082, 3083, and 3084 dosed with 3.0 mg/kg, showed that 53/983 patients (5.4%) were positive for treatment-emergent ADA with titers ranging from 1:1 to 1:106. Twenty-seven of these patients (50%) had transient responses. Transient responses were defined by the sponsor as those that are positive at only one time point. In the long-term, open-label study, C38072/3085, using the 3.0 mg/kg dose, 49/1014 (4.8%) patients developed ADA with titers ranging from 1:2 to 1:33. ADA were transient in 20 (41%) patients. The incidence of hypersensitivity reactions that occurred during drug infusion in reslizumab treated patients (30%) is similar to that seen with placebo-treated patients (39%).

The basis for such hypersensitivity reactions is not known, however hypersensitivity reactions may be more common in patients with eosinophilic asthma than in the general population. Overall, the reported rate of adverse events for pivotal studies was similar between the ADA positive (65%) and ADA negative (67%) patients. No information on neutralizing antibodies was provided, as the assay is currently under development. However there appears to be no association between the presence of anti-drug antibodies and either loss of efficacy or increased levels of adverse events (table 48 below).

Table 48: Number of Anti-Drug Antibody Positive and Negative Patients in Cohort 3

Variable Subset	Number (%) of patients		
	Reslizumab 3.0 mg/kg (N=1028)	Reslizumab 0.3 mg/kg (N=103)	All reslizumab (N=1131)
Treatment-emergent ADA positive			
Yes	69 (7)	12 (12)	81 (7)
No	959 (93)	91 (88)	1050 (93)

Source: ISS Summary 2.1.1

The overall adverse event profile also appears similar between ADA positive and ADA negative patients (Table 49).

Table 49: Most Common Adverse Events (at Least 5% in Any Treatment Group) by ADA Status and Treatment Group Safety Analysis Set Cohort 3

MedDRA Preferred Term	Number (%) of ADA-positive patients		Number (%) of ADA-negative patients	
	All Reslizumab (N=81)	Reslizumab 3.0 mg/kg (N=69)	All Reslizumab (N=1050)	Reslizumab 3.0 mg/kg (N=959)
Patients with at least 1 event	52 (64)	45 (65)	697 (66)	645 (67)
Asthma	12 (15)	12 (17)	226 (22)	220 (23)
Nasopharyngitis	10 (12)	10 (14)	99 (9)	93 (10)
Headache	5 (6)	5 (7)	81 (8)	73 (8)
Sinusitis	5 (6)	5 (7)	55 (5)	52 (5)
Upper respiratory tract infection	5 (6)	5 (7)	94 (9)	91 (9)
Dyspnoea	4 (5)	4 (6)	19 (2)	18 (2)
Oropharyngeal pain	4 (5)	4 (6)	24 (2)	1 (1)

Source: ISS Summary 7.18.3.

ADA=antidrug antibody; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in treatment group.

The applicant reported six anaphylactic reactions in the asthma clinical program. Of these, four cases had a temporal link to infusion of 3mg/kg of reslizumab. These were observed in four female patients, two from study C3802/3083, one from study 3082 and one from 3084. The four patients with treatment –related anaphylaxis tested anti-drug-IgG negative but were not tested for product specific IgE. The product-specific IgE (b) (4) is currently under development by the applicant. There was also one placebo patient from study 3083 that suffered an episode of anaphylaxis. Two of the patients had medical histories of hypersensitivity/anaphylaxis to multiple allergens; the third had a history of drug sensitivities. The fourth was an adjudicated case and the predisposing factors are still unclear. Most of these patients can be considered to have a predisposition to hypersensitivity reactions. The applicant reported no other drug-related anaphylaxis in either the long-term extension of the 3.0 mg/kg-dose or the other clinical studies in conducted as part of the reslizumab development program.

Summary Table: Product related factors that could impact development of immunogenicity and hypersensitivity.

Drug Product Batch Number	Drug Substance Batch Used to Make Drug Product	Clinical Use
11-002802	89991 + 202709	Phase 3 (BREATH program)
11-002803	202709	Phase 1 (C38072/1107) and Phase 3 (BREATH program)
11-000701	89170	Phase 3 (BREATH program)
10-000862	89170	Phase 1 (C38072/1102) and Phase 3 (BREATH program)
10-001036	89182	Phase 2 (5-0004) and Phase 3 (BREATH program)
0807015	67677	Phase 2 (5-0004)
0706015	52758	Phase 2 (5-0002, 5-0004, and 5-00010)
0712025	07P01367	Phase 2 (5-0002, 5-0004, and 5-00010)

(b) (4)

Table prepared by DS reviewer Ramesh Potla.

Product-related factors in reslizumab may impact immunogenicity and affect the incidence of anaphylaxis. These factors include glycosylation, residual nucleic acids and host cell proteins from the cell substrate used to manufacture reslizumab, (b) (4)

The product is produced in the NSO murine cell line, and this cell line is known to introduce the carbohydrate sequence galactose-alpha1, 3-galactose (alpha-gal) into the carbohydrate side-chains of the monoclonal antibody during the glycosylation process. Glycoproteins with the alpha-gal carbohydrate sequence are commonly produced by most mammals but not by Old World monkeys, apes, and humans due to lack of expression of the enzyme alpha-1, 3-galactosyl transferase (alpha-1, 3GT)

that is responsible for the addition of alpha-gal to glycoproteins⁵. As a result, alpha-gal containing glycoproteins are highly immunogenic in humans, with as much as 1% of natural antibodies in sera, primarily IgG and IgM, being specific for this carbohydrate⁶. This is in part due to exposure to gut flora which have the ability to add alpha-gal to their glycoprotein and glycolipid molecules, and in part through dietary exposure. While the majority of the human population has anti-alpha-gal IgG antibodies in their sera, a proportion of the population develops IgE antibodies specific for alpha-gal, and these antibodies are associated with allergies to meat products, and tick bites. IgE to alpha-gal has also been implicated in anaphylactic responses in colorectal cancer patients treated with cetuximab, an anti-Epidermal Growth Factor Receptor monoclonal antibody⁷. Cetuximab is produced in Sp2/02 murine hybridoma cells, which also glycosylate proteins with alpha-gal-containing carbohydrates. The prevalence of hypersensitivity to cetuximab had a regional distribution strongest in southeastern United States and was associated with pre-existing IgE antibodies to alpha-gal. Three out of the four reslizumab-associated anaphylaxis cases occurred in geographical areas where tick allergies are known to arise. Although the patients tested negative for ADA in the screening assay, the available immunogenicity assays have a reported sensitivity of ~22 ng/ml, which is too high to reliably detect antigen specific serum IgE. Levels of antigen-specific IgE in sera are typically present in the low nanogram to high picogram per ml range. Recently the applicant had the sera of the four anaphylactic patients evaluated for anti-alpha gal IgE antibodies and reported negative findings. This information is still under review by the Agency and will be address in an addendum to the current report. Currently, the possibility that the anaphylactic responses were triggered by pre-existing sensitivities to alpha-gal remains an open question. Of note, mepolizumab, a recently approved humanized IgG1 produced in CHO cells, also specific for IL-5 and used to treat similar patient population of asthmatics had no reported cases of anaphylaxis. CHO cells are of Chinese Hamster origin and are the primary production system for licensed therapeutic monoclonals. This suggests that in addition to factors intrinsic to the study population, product specific factors are likely playing a role in the reslizumab-associated anaphylactic events.

Besides product glycosylation, the residual levels of NS/0 derived host cell proteins and nucleic acids may also enhance product immunogenicity by potentially acting as adjuvants, or by stimulating pre-existing cross-reactive IgE responses to mouse proteins resulting in anaphylaxis. An impact of host cell derived impurities in the immunogenicity of a biologic was shown for Omnitrope where high concentrations of host cell proteins were associated with increased immunogenicity rates⁸. Omnitrope is a recombinant

⁵ B.A. Macher, U. Galili. The Galalpha1, 3-Gal-beta-1, 4-GlcNAc-R (alpha-Gal) epitope: a carbohydrate of unique evolution and clinical relevance *Biochim. Biophys. Acta* (2008), 1780:75–88

⁶ U. Galili, F. Anaraki, A. Thall, C. Hill-Black, M. Radic, One percent of human circulating B lymphocytes are capable of producing the natural anti-Gal antibody, *Blood* (1993), 82:2485–2493.

⁷ Commins SP, TA Platts-Mill Delayed anaphylaxis to red meat in patients with IgE specific for galactose alpha-1, 3-galactose (alpha-gal). *Curr Allergy Asthma Rep.* (2013), 13:72-7.

⁸ Thakrar K., Pr. Bodalia, A. Grosso. Assessing the safety of Omnitrope in Europe. *Brit Med J Clin Pharm* (2010), 2: 298-301.

human growth hormone commercialized in Europe and in the United States. Once additional purification steps were added to the manufacturing process to reduce the level of residual host cell impurities, the immunogenicity rates in subsequent clinical studies were reduced for this product.

The contribution of host cell-derived impurities to reslizumab anaphylaxis is unclear at this time. The residual amount of host cell proteins and nucleic acids and alpha-gal measured by the applicant in reslizumab clinical lots, are consistent for the lots used across the pivotal efficacy studies. Residual amounts of host cell proteins and nucleic acids are within the range expected for biotechnology products produced in murine cell lines. Currently there are eight licensed monoclonal antibodies manufactured in NS/0 cells and five monoclonals produced in Sp2/0, and all but one, have a reported incidence of anaphylaxis. However, there are seven other approved monoclonal antibodies produced in CHO cells that also have reported cases of anaphylaxis, albeit at lower incidence rates, despite CHO cells typically not expressing the α -1, 3GT enzyme responsible for the addition of alpha-gal during glycosylation⁹. Thus monoclonal antibody-triggered anaphylaxis is not restricted to products produced in murine cell lines.

(b) (4)

In summary, there are product-specific and patient-specific factors that could be contributing to the anaphylaxis adverse events observed in the phase 3 clinical studies in eosinophilic asthma patients. The applicant did not adequately investigate the root causes of the anaphylactic events. Therefore, the product safety profile is not well understood at this time.

Advisory Committee Results

The Pulmonary -Allergy Drugs Advisory Committee met on December 9th, 2015. An immunogenicity briefing based on this review's findings was presented to the committee. The meeting voted 11 to 3 in favor of approval of the product for the adult indication. The committee did express reservations concerning the safety signals observed, and favored additional studies in the US and pediatric populations.

Prior to the advisory committee meeting the applicant submitted new data analyzing the anti-alpha gal IgE levels in the sera of four treatment-related anaphylaxis patients. The applicant tested baseline and post-event serum samples at the (b) (4) commercial laboratory. This laboratory used a proprietary anti-alpha gal ELISA developed by (b) (4). The ELISA is not cleared by CDRH. The assay is a solid phase immunoassay with a reported sensitivity of (b) (4) which is within the

⁹ Guan M., YP Zhou, JL Sun, SC Chen; Adverse events of Monoclonal Antibodies used for Cancer Therapy. Biomed Res Int. (2015) , 2015:428169

acceptable sensitivity range for antigen specific IgE. (b) (4)

(b) (4)

No suitable qualification report was submitted to the Agency concerning the anti-alpha gal IgE ELISA and this will be a PMC.

Table 1: Serum Sample Test Results

Subject, Study, country	Supplemental History	Anaphylaxis	ADA Serum Sample Tested	Alpha Gal IgE (kU/L) ¹	Total IgE (IU/mL)
370307, 3083, Germany Hamburg	No history of potential exposure to ticks; no history of allergies to red meat	Week 4 (2 nd infusion) Reported by investigator as anaphylactic reaction	Baseline (Visit 2)	(b) (4)	(b) (4)
			Early Termination 25 days after anaphylaxis		
370312, 3083, Germany Hamburg	No history of potential exposure to ticks; no history of allergies to red meat	Week 44 (12 th infusion) Reported by investigator as anaphylactic reaction	Baseline (Visit 2)	(b) (4)	(b) (4)
			Early Termination 1 days after anaphylaxis		
831404, 3084, USA, NY	No history of potential exposure to ticks; no history of allergies to red meat	Week 4 (2 nd infusion) Reported by investigator as anaphylactic reaction	Baseline (Visit 1.1 / Pre)	(b) (4)	(b) (4)
			Early Termination 41 days after anaphylaxis		
782205, 3082, Thailand	No history of potential exposure to ticks; no history of allergies to red meat	Week 44 (Day after 12 th infusion) Adjudicated by external committee as highly likely anaphylactic reaction	Baseline (Visit 2)	(b) (4)	(b) (4)
			Week: 48 (Visit 14) 20 days after anaphylaxis		

¹ Serum samples diluted 1:3 prior to testing.
ADA=anti-drug antibody.

Proposed Immunogenicity Label in 6.2

“In placebo-controlled trials, a *treatment-emergent* anti-reslizumab antibody response developed in 53/983 (b) (4) (0%) (b) (4) 3 mg/kg. In the long-term, open-label study, (b) (4) anti-reslizumab antibody (b) (4) detected in 49/1014 (b) (4) (0%) (b) (4) 3 mg/kg (b) (4) 36 months. There was no detectable impact of the antibodies on the clinical pharmacokinetics, pharmacodynamics, efficacy or safety of CINQAIR [see Clinical Pharmacology (12.2)].

The data reflect the percentage of patients whose test results were positive for antibodies to reslizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to reslizumab with the incidence of antibodies to other products may be misleading.”

Reviewer comment:

The clinical team requested the applicant to substantially re-write the label using the approved label from BLA 125526 (mepolizumab) as an example.

The immunogenicity information in the above label is accurate, but is missing information. The italicized words are added by immunogenicity reviewer as qualifiers for the specific statements. The applicant should also include:

- *Include the term “treatment-emergent” and “detectable impact” in this section.*
- *An initial statement as per labelling tool that Biologics can be immunogenic.*
- *A statement that “neutralizing antibodies were not evaluated”.*
- *A comment on treatment-related anaphylaxis and product-specific IgE antibodies when that data is available.*

PMR/PMCs

The following immunogenicity-related PMR and PMCs are proposed:

PMR:

1. Develop and validate a sufficiently sensitive product specific anti-IgE antibody assay to test sera from all treatment-associated anaphylaxis patients for the presence of anti-reslizumab IgE antibodies. Submit the immunoassay validation report by December of 2016.
2. To test sera from all treatment associated anaphylaxis patients for the presence of anti-reslizumab IgE antibodies using the product-specific anti-IgE antibody assay developed as part of immunogenicity PMR#1. Submit the final clinical study report by March, 2017.

PMCs:

1. Develop and validate a neutralizing antibody assay to test sera from confirmed anti-drug antibody positive asthmatic patients. Submit the immunoassay validation report by December, 2016.
2. Submit a qualification report demonstrating the suitability of the commercial anti-alpha gal ELISA from (b) (4) used to analyze the sera of the four treatment-related anaphylaxis patients. Submit the final clinical study report by March, 2017

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/s/

JOAO A PEDRAS VASCONCEL

12/18/2015

Primary immunogenicity quality review for BLA 761033 reslizumab

LABEL AND LABELING REVIEW

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

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

Date of This Review: 10/27/2015

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: BLA 761033

Product Name and Strength: Cinqair (reslizumab) Injection, 100 mg/10 ml

Product Type: Single Ingredient

Rx or OTC: Rx

Applicant/Sponsor Name: Teva Branded Pharmaceutical Products R&D, Inc.

Submission Date: 3/29/2015 and 7/27/2015

OSE RCM #: 2015-1251

DMEPA Primary Reviewer: Hina Mehta, PharmD

DMEPA Team Leader: Kendra Worthy, PharmD

1 REASON FOR REVIEW

Teva Branded Pharmaceutical Products R & D, Inc. submitted BLA 761033 for Cinqair (reslizumab) injection. Thus, the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) requested we evaluate the container labels, carton labeling, and prescribing information for vulnerabilities that could lead to medication errors.

2 MATERIALS REVIEWED

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

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A-C
ISMP Newsletters	N/A-D
FDA Adverse Event Reporting System (FAERS)*	N/A-E
Other	N/A-F
Labels and Labeling	G

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

We performed a risk assessment of the proposed container labels, carton labeling, and prescribing information to identify deficiencies that may lead to medication errors and other areas of improvement.

Container Labels and Carton Labeling

Our review of the container labels identified areas of improvement to increase clarity and prominence of important information. Thus, we make recommendations in Section 4.2.

Prescribing Information

Our review of the prescribing information identified areas of improvement to increase clarity and prominence of important information. Thus, we make recommendations in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

DMEPA recommends the following be implemented prior to the approval of the application.

4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Highlights Of Prescribing Information, Dosage and Administration Section
1. To increase the prominence of important information we recommend adding the statement “Do not administer as an intravenous push or bolus” after the statement “CINQAIR is for intravenous (b) (4) infusion only”. Additionally remove the abbreviation (b) (4) in parenthesis.¹
 2. In order to be consistent with the Full Prescribing Information section we recommend adding the statement “CINQAIR should be administered by a healthcare professional prepared to manage anaphylaxis”.
- B. Dosage Forms and Strengths Section, Highlights of Prescribing Information
1. To mitigate confusion, we recommend revising the statement “(b) (4)” to (b) (4) per USP guidelines.
- C. Full Prescribing Information, Dosage and Administration Section 2, Administration Instructions
1. In section 2.1 Dosing remove the abbreviation (b) (4) in parenthesis in the first sentence.
 2. Under section 2.2 Administration Instructions move the statement “CINQAIR should be administered by a healthcare professional prepared to manage anaphylaxis” to step 1.
 3. Under Section 2.2 Administration Instructions the third statement “Use an infusion set with an in-line, (b) (4) low-protein-binding filter (pore size of 0.22 µm).” (b) (4) We recommend moving this statement as a separate step and listing it as step 3 to increase the prominence of this important information.

4.2 RECOMMENDATIONS FOR TEVA

We recommend the following be implemented prior to approval of this BLA 761033:

- A. Container Label and Carton Labeling
1. Replace “Tradename” with conditionally accepted proprietary name, Cinqair, throughout all labels and labeling.
 2. Present the names on the carton per display below:

¹ Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

Tradename
(reslizumab)
Injection

Please refer to 21 CFR 201.10(g)(2)

3. Present the strength as total quantity per total volume followed by the concentration per milliliter (mL) in accordance with USP General Chapter <1>. For example, 100 mg/10 ml (10 mg/ml).
4. Revise the statement “ (b) (4) to “For Intravenous Infusion Only Dilute Prior to Administration”. We recommend this to minimize the risk of administering the drug as an intravenous bolus.
5. On side panel immediately preceding storage recommendations add and bold statement “**Must be Refrigerated**”. We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked. Consider moving other information to other side panel if needed to add the statement.
6. Place “One Single Use Vial” before the “Discard Unused Portion” statement to maintain consistency with other labels and labeling.
7. As currently presented the Principal Display Panel is cluttered which may affect readability of pertinent information. Consider reducing the size of the graphic.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for reslizumab that Teva Branded Pharmaceutical Products R&D submitted on 3/29/2015.

Table 2. Relevant Product Information for reslizumab	
Initial Approval Date	N/A
Active Ingredient	Reslizumab
Indication	To reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids
Route of Administration	Intravenous Infusion
Dosage Form	Solution for Injection
Strength	100 mg/ 10 ml (10 mg/ml)
Dose and Frequency	3 mg/kg delivered every 4 weeks
How Supplied	Single-use 10 ml vial, 100mg
Storage	Refrigerated at 2-8 °C (36-46°F) Diluted in Normal Saline: 2-8 °C (36-46°F) or at room temperature up to 25°C (77°F), protected from light for up to 16 hours
Container Closure	Single use vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

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

B.2 Results

Our search identified three previous reviews, and we confirmed that none of these are applicable to this review.

OSE RCM# or Panorama#	Review Date	Summary of Recommendations
2008-858 ²	2/6/2009	The review evaluates the proprietary name for reslizumab that was submitted by the applicant. The name was conditionally acceptable.
2014-26293 ³	2/25/2015	The review evaluates the proprietary name for reslizumab that was submitted by the applicant. The name was denied.
2015-80126 ⁴	6/17/2015	The review evaluates the proprietary name for reslizumab that was submitted by the applicant. The original proprietary name conditionally accepted under RCM# 2008-858 was withdrawn by the applicant. The name submitted under Panorama# 2015-80126 was acceptable.

² Cantin, L. Proprietary Name Review for rezlizumab (IND (b) (4)). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2009 FEB 06. RCM No.: 2008-858.

³ Barlow, M. Proprietary Name Review for rezlizumab (IND 101399). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 FEB 25. Panorama No.: 2014-26293

⁴ Owens, L. Proprietary Name Review for rezlizumab (BLA 761033). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JUN 17. Panorama No.: 2015-80126

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,⁵ along with postmarket medication error data, we reviewed the following reslizumab labels and labeling submitted by Teva on 3/30/2015 and 7/27/2015.

- Container label
- Carton labeling
- Prescribing Information Labeling

G.2 Label and Labeling Images

(b) (4)

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

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

HINA S MEHTA
10/27/2015

KENDRA C WORTHY
10/27/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 16, 2015

TO: Colette Jackson, Regulatory Project Manager
Kathleen Donohue, M.D., Medical Officer
Banu Karimi-Shah, M.D., Cross Discipline Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 761033

APPLICANT:
DRUG: reslizumab

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATIONS: Treatment of eosinophilic asthma

CONSULTATION REQUEST DATE (signed): July 2, 2015

INSPECTION SUMMARY GOAL DATE (original): December 3, 2015
DIVISION ACTION GOAL DATE March 28, 2016
PDUFA DATE: March 28, 2016

I. BACKGROUND:

IL-5 is a key cytokine responsible for the differentiation, maturation, recruitment, and activation of human eosinophils. Reslizumab is a humanized anti-IL-5 monoclonal antibody of the immunoglobulin G/4κ (IgG4/κ) isotype that acts by binding circulating IL-5 and preventing binding to the IL-5 receptor. The sponsor has proposed that intravenous reslizumab may have potential efficacy and safety profile for treatment of patients with eosinophilic asthma (a blood eosinophil count of at least 400 per microliter) with airway reversibility of at least 12% following short-acting beta-agonist administration.

CDER DPARP requested that a sponsor inspection be conducted. No clinical study sites were requested because the recruitment was widely distributed globally, with each site enrolling only a small number of patients. Three clinical trials (Study C38072-3082, Study C38072-3083 and C38072-Study 3084) were part of the applicant's BLA that were subject of this sponsor inspection.

Study C38072-3082

Study C38072-3082 was a randomized, double-blind, placebo fixed-group study to evaluate the efficacy and safety of reslizumab in the reduction of asthma exacerbations in subjects with eosinophilic asthma. The primary objective of this study was to demonstrate the efficacy of reslizumab, at a dose of 3 mg/kg administered intravenously every four weeks over 12 months, as assessed by the reduction in frequency of clinical asthma exacerbations (CAEs) during 12 months.

An exacerbation event was considered a CAE if the subject met either or both of the criteria, and corroborated with at least one other measurement to indicate the worsening of clinical signs and symptoms of asthma [(1) use of systemic, or (2) an increase in the use of inhaled, corticosteroid treatment for three or more days (a two-fold increase for at least three days for patients already on systemic or inhaled corticosteroids) or asthma-related emergency treatment]. The above criteria must be corroborated by a decrease in the forced expiratory volume in 1 second (FEV1) by 20% or more from baseline, a decrease in the peak expiratory flow rate by 30% or more from baseline on two consecutive days, or worsening of symptoms or other clinical signs per physician evaluation of the event. The primary efficacy measure for this study was the frequency of CAEs reported for each subject during the 52-week treatment period.

Study C38072-3083

Study C38072-3083 was similar to Study 3082. The primary objective of this study was to determine whether reslizumab, at a dose of 3 mg/kg administered intravenously every

four weeks over 12 months, was more effective than placebo in reducing the number of clinical asthma exacerbations (CAEs) in subjects with eosinophilic asthma as assessed by the frequency of CAEs.

An exacerbation event was considered a CAE if the subject met either or both criteria and was corroborated with at least one other measurement to indicate the worsening of clinical signs and symptoms of asthma [(1) use of systemic, or (2) an increase in the use of inhaled, corticosteroid treatment for three or more days (a two-fold increase for at least three days for patients already on systemic or inhaled corticosteroids) or asthma-related emergency treatment]. The above criteria had to be corroborated by spirometric, clinical symptoms, or other clinical signs per physician evaluation of the event. The primary efficacy measure for this study was the frequency of CAEs reported for each patient during the 52-week treatment period.

Study C38072-3084

Study C38072-3084 was a 16-week, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of reslizumab (3.0 mg/kg) treatment in subjects with moderate to severe asthma. The primary study objective was to characterize the efficacy of reslizumab treatment at a dosage of 3.0 mg/kg every four weeks for a total of four doses in improving pulmonary function in relation to baseline blood eosinophil levels in patients with moderate to severe asthma as assessed by the change from baseline to week 16 in forced expiratory volume in 1 second (FEV1). The primary efficacy endpoint for this study was FEV1 as assessed at week 16.

II. RESULTS:

Name of CI Location	Study Site/Protocol	Inspection Date	Classification*
Sponsor: Teva Pharmaceutical Industries Ltd 41 Moores Road Frazer, PA 19355	Protocol Study C38072/3082	September 28- October 2, 2015	Preliminary: NAI
	Protocol Study C38072/3083		
	Protocol Study C38072/3084		

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

SPONSOR

Teva Pharmaceutical Industries Ltd

Philadelphia, PA

a. What was inspected:

The inspection was conducted from September 28-October 2, 2015. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

Monitoring deficiencies, in terms of initiating interim monitoring visits within a timely manner, were identified. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was not issued at the end of the sponsor inspection.

Reviewer's Comment: *On August 28, 2015, the DPARP sent OSI four specific questions, raised during clinical review, which were discussed with ORA prior to the field inspection. The four items below provided by DPARP helped OSI focus and refine the inspection for ORA. Please find below the four questions submitted by CDER DPARP to OSI, prior to the start of the inspection by ORA.*

1. Examine the changes made to Study 3082 and Study 3083 when the database was unlocked to correct some variables. The following application timeline sequence was as follows: (1) May 22, 2014: database lock, (2) August 8, 2014: Statistical Analysis Plan finalized, (3) August 18, 2014: study unblinding, (4) September 26, 2014: database "unlock" to fix some fields, and (5) October 3, 2014: database re-lock.

Inspection results:

There were two "Post Lock Discrepancy Logs" to document changes made to the clinical database after the database "unlock" occurred on September 26, 2014.

The clinical database field AEACNOTH (a SAS annotated variable "Other Action Taken" on the AE CRF page) was added to the database but was never incorporated into the final locked SDTM (Study Data Tabulation Module) for Study 3082 and Study 3083.

For Study 3082 *only*: Subject 3082_185201 Week #32 FVC value was incorrectly entered as 63.2 L, and this was corrected by the study site.

For Study 3083 *only*: Subject 3083_371301 Week #44 FVC value was incorrectly entered as 111.1 L, and this was corrected by the study site. Further, the German study site database demographic fields "AGE" (age) and "YEAR" (birthdate) were added. Since these issues were identified after database lock and unblinding, the above missing database fields were added to the SDTM AE dataset.

2. Determine how a clinical asthma exacerbation was captured and coded for Study 3082 and Study 3083. In DPARP's review, the CRF did not seem to capture asthma exacerbation precisely. For example, the CRF had one checkbox for "emergency treatment because of asthma". However, this field variable generates two variables in the analysis dataset, "unscheduled visit to the physician's office" and "visit to the emergency room". If there was an adjudication process, how was this determined?

Inspection results:

I. Adjudication Process

A single Clinical Endpoints Adjudication Committee for Study 3082 and Study 3083. (b) (4) contracted the following clinicians as reviewers:

- (a) (b) (4)
- (b) (b) (4)
- (c) (b) (4)

The Adjudication Management Plan contained a dossier for clinical exacerbation of asthma, including: office notes; spirometry results; peak flow meters; medication lists; ER notes, if applicable; discharge summary, if applicable; history and physical, if applicable; relevant diagnostics such as chest x-ray and CT, if applicable; additional records for death events (death summary, death certificate, and autopsy report, if available), and supplemental information from the e-CRFS (such as clinical asthma exacerbation; asthma history; allergy history; airway reversibility (completed only at screening visit); physical exam (near onset of the event); pulmonary function tests (baseline and near the onset of the event); Asthma Control Questionnaire (baseline and near the onset of the event); Asthma Symptom Utility Index (baseline and near the onset of the event); Asthma Quality of Life Questionnaire (baseline and near the onset of the event); beta agonist usage (baseline and near the onset of the event); treatment completion; study completion; concomitant medications).

Members of the Clinical Endpoints Adjudication Committee were notified of the events for review, and the above dossier was made available to the committee. The Committee independently reviewed and documented the adjudication decision and rationale. If needed, the Committee could issue a query to (b) (4) to complete the adjudication decision through the electronic adjudication system. Subsequently the Committee met in full committee review meetings to discuss discordant cases and render final adjudication outcome.

II. Miscellaneous

The FDA inspector reviewed the Clinical Endpoints Adjudication Committee electronic records for Protocol 3082 (Site 063 - Dr. Fuentes) for all five subjects and Site 3083 (Site 363 - Dr. Korn) for six randomly selected subjects of the 22 randomized subjects. There were no data discrepancies noted.

3. Determine if the 15 subjects from Study 3084 Sites 864 and Site 909 who were excluded from the safety database had adverse events?

Inspection results:

The following subjects from these two sites were discontinued because of adverse events: Subject 864407 (acute urticaria), Subject 864412 (asthma exacerbation) and Subject 864404 (acute bronchospasm), and Subject 864403 (asthma exacerbation. Note: This subject was “lost to follow-up” in the FDA patient data line listings).

The sponsor master note to file (September 13, 2013) regarding rationale and decision to exclude Site 864 and Site 909 data from safety and efficacy analyses, and the e-CRFs for the enrolled subjects at these two discontinued clinical sites were provided to the FDA during the inspection.

Reviewer’s Comment:

These sites were discussed in the BLA submission to the Agency in the Clinical Study Report, Section 9.7.1.1.1. Sites Excluded from Analysis. Prior to the submission, sponsor also communicated these two site closures to the FDA in a letter to CDER DPARP on August 13, 2013, and June 5, 2013.

4. Assess anaphylaxis and myositis/muscle damage/elevated creatine phosphokinase (CPK) which emerged as important safety signals during DPARP’s review.

Inspection results:

An Excel spreadsheet output of the clinical AE search for Study 3082, Study 3083, and Study 3084 were provided to the FDA during the inspection. The monitoring site visit reports for the 12 clinical sites covered in this FDA sponsor inspection did not show any instances of reports of clinically significant events that involved these AE terms.

Reviewer’s Comment: *OSI reviewer discussed the above preliminary FDA inspectional results with the DPARP Medical Team. DPARP also sent Information Requests (IRs), to address the above questions. Further, the DPARP Medical Team has requested from the sponsor datasets to independently address Item #4, which could be an evolving DPARP review issue.*

c. Assessment of data integrity: The inspection at the sponsor site did not have any impact on data reliability. Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The sponsor (Teva) was inspected. The sponsor's three clinical studies, Study C38072-3082, Study C38072-3083 and Study C38072-3084 were inspected as part of this BLA. The preliminary regulatory classification for the sponsor inspection is No Action Indicated (NAI).

In summary, data received from the audited sponsor site appear acceptable in support of the BLA.

Note: The inspectional observation is based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly upon receipt and review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

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

/s/

ANTHONY J ORENCIA
10/16/2015

SUSAN D THOMPSON
10/16/2015

KASSA AYALEW
10/16/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 761033	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Established/Proper Name: reslizumab Dosage Form: injection Strengths: 3 mg/kg		
Applicant: Teva Pharmaceuticals Agent for Applicant (if applicable):		
Date of Application: March 29, 3015 Date of Receipt: March 30, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: March 30, 2016		Action Goal Date (if different):
Filing Date: May 29, 2015		Date of Filing Meeting: May 11, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication: To reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<i>The application will be a priority review if:</i>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<i>• 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)</i>	
<i>• The product is a Qualified Infectious Disease Product (QIDP)</i>	
<i>• A Tropical Disease Priority Review Voucher was submitted</i>	
<i>• A Pediatric Rare Disease Priority Review Voucher was submitted</i>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
<input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC	
Other:	

Collaborative Review Division (if OTC product):

List referenced IND Number(s): 101399, and (b) (4)

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</i>	<input type="checkbox"/>	<input type="checkbox"/>			
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Email received from manager on 4/2/2015 acknowledging the request.

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance? ¹ If not, explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

2

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

Version: 4/14/2015

7

<i>(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.</i>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

3

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

Version: 4/14/2015

8

Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

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

5

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

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): August 18, 2010	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Included in BLA submission
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): January 15, 2015	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Included in BLA submission
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s): CAC dated February 25, 2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 11, 2015

BACKGROUND: Teva is submitting an original BLA for reslizumab for the indication to reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Colette Jackson	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Banu Karimi-Shah		Y
Division Director/Deputy	Badrul Chowdhury Lydia Gilbert-McClain		Y/N
Office Director/Deputy	Curtis Rosebraugh Mary Parks		N
Clinical	Reviewer:	Kathleen Donohue	Y
	TL:	Banu Karimi-Shah	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Yunzhao Ren	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	Len Zeng	Y
	TL:	David Petullo	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Carol Galvis	Y
	TL:	Marcie Wood	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Maria Gutierrez Lugo	Y
	RBPM:	Andrew Shiber	N
• Drug Substance	Reviewer:	Ramesh Potla	Y
• Drug Product	Reviewer:	Tracy Denison	Y
• Process	Reviewer:	Bo Chi	Y
• Microbiology	Reviewer:	Lakshmi Rani Narasimhan	Y
• Facility	Reviewer:	Steven Fong	Y
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:	Tracy Denison	Y
• Labeling (BLAs only)	Reviewer:	Jibril Abdus-Samad	Y
• Other (e.g., Branch Chiefs, EA Reviewer)			
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines	Reviewer:		
	TL:		
Other attendees			

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p>CLINICAL</p> <p>Comments: Comment to be relayed in the 74-day letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIostatISTICS</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: PMHS consult needed for Section 8.1 of the label	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>New Molecular Entity (NDAs only)</u> • Is the product an NME?	<input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments: IR forthcoming to be sent to the company by the OBQ RPM	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CMC Labeling Review (BLAs only)</p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<p><input type="checkbox"/> N/A</p> <p><input type="checkbox"/> YES <input checked="" type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<p>Signatory Authority: Curtis Rosebraugh, M.D., Director, ODE II</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): August 28, 2015</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p>	

Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

COLETTE C JACKSON
08/14/2015

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

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: BLA 761033

Application Type: New BLA

Name of Drug/Dosage Form: Reslizumab, IV

Applicant: Teva Pharmaceuticals

Receipt Date: March 30, 2015

Goal Date: March 30, 2016

1. Regulatory History and Applicant's Main Proposals

Teva Pharmaceuticals submitted a new biologic application for reslizumab, a humanized monoclonal antibody (IgG4kappa) with a proposed indication to reduce exacerbations, relieve symptoms and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids. In this new application, Teva submitted the prescribing information, patient information sheet, and carton and container labels.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by July 1, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. **Instructions to complete this item:** If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- NO** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *Established pharmacologic class is not included in the statement. Will send comment in 74-day letter*

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

Selected Requirements of Prescribing Information

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- NO** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *Teva has not correctly titled subsections 8.2 and 8.3 and is not in accordance with 21CFR 201.56(d)(1). Teva has added additional subsections not outlined in the CFR. Comments to be relayed in 74-day letter.*

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*]” or “[see *Warnings and Precautions (5.2)*]”.

Selected Requirements of Prescribing Information

Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

YES

Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES**
42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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

/s/

COLETTE C JACKSON
08/14/2015