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RESEARCH**

APPLICATION NUMBER:

761070Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE
For 506B Reportable¹ PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the [instructions](#) (see Appendix A) and by referring to [MAPP 6010.9](#), “Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements.”

Note: Do *not* use this template for CMC PMCs. Instead, use the CMC PMC Development Template.¹

SECTION A: Administrative Information

NDA/BLA/Supplement # **BLA # 761070**
PMR/PMC Set (####-#)
Product Name: **Benralizumab**
Applicant Name: **AstraZeneca**
ODE/Division: **ODE II/DPARP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct an open-label, pharmacokinetic and pharmacodynamics study of benralizumab in pediatric patients 6 to 11 years of age with a continued safety evaluation out to a minimum of 48 weeks.

2. PMR/PMC Schedule Milestones^{2, 3}

Draft Protocol Submission:	06/2018
Final Protocol Submission:	10/2018
Study/Trial Completion:	05/2022
Interim /Other:	NA
Final Report Submission:	12/2022

¹ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

² *Final protocol, study/trial completion, and final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

³ Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study⁴ or clinical trial⁵ in the text box below.

The goal of this study is to evaluate the pharmacokinetics and pharmacodynamics of benralizumab in patients 6 to 11 years of age. Safety and efficacy information will also be collected.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- Subpart I or H (animal efficacy rule) PMR:** Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- Subpart H or E (accelerated approval) PMR:** Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit *[Skip to Q.5]*
- PREA PMR:** Meets PREA postmarketing pediatric study *requirements [Skip to Q.5]*
- FDAAA PMR (safety):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial *[Go to Q.3]*
- PMC (506B reportable):** Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H, H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. *[Go to Q.3]*

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- Longer-term data needed to further characterize the safety/efficacy of the drug
- Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- Study/trial is to further explore a theoretical concern that does not impact the approval determination
- Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

⁴ A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

⁵ A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** [for PMCs skip to Q.5]. Complete this entire section

a. The purpose of the study/clinical trial is to: [Select one, then go to Q.4.b]

- Assess a known serious risk related to the use of the drug
- Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS⁶ and Sentinel's postmarket ARIA⁷ system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

⁶ FDA Adverse Event Reporting System (FAERS)

⁷ Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- Cannot identify exposure to the drug(s) of interest in the database.
- Serious risk (adverse event) of concern cannot be identified in the database.
- The population(s) of interest cannot be identified in the database.
- Long-term follow-up information required to assess the serious risk are not available in the database.
- Important confounders or covariates are not available or well represented in the database.
- The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either “Yes” or “No” and provide the appropriate responses.]

Yes, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

[Explain why a study is sufficient]

No, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- Other

[If you selected “other,” expand on the reason(s) why a study is not sufficient.]

f. **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs:** What type of study or clinical trial is needed to achieve the goal described in Q1 or Q4.a above?

[Select ONE OPTION only under either “Type of Study” or “Type of clinical Trial”]

TYPE OF STUDY

- Drug interaction or bioavailability studies (nonclinical only)
- Epidemiologic (observational) study related to safe drug use
- Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Immunogenicity study (nonclinical)
- Meta-analysis or pooled analysis of previous observational studies
- Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
- Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
- Pharmacogenetic or pharmacogenomic study
- Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
- Quality CMC study (e.g., manufacturing, studies on impurities)
- Quality stability study
- Registry-based observational study

TYPE OF STUDY

Other (describe) _____

TYPE OF CLINICAL TRIAL

- Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
- Dose-response clinical trial
- Dosing trial (e.g., alternative dosing schedule)
- Drug interaction or bioavailability clinical trial (clinical only)
- Immunogenicity trial (clinical)
- Meta-analysis or pooled analysis of previous clinical trials
- Pharmacogenetic or pharmacogenomic clinical trial
- Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
- Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
- Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
- Safety outcomes trial (SOT)**
- Thorough Q-T clinical trial
- Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as “studies.” However, for the purposes of this template, PREA investigations are categorized according to the established definitions of “studies” and “trials” (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

[SECTION D: PMR/PMC Additional Information](#)

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

- Yes
- No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):

[Select all that apply]

- For *non-PREA* pediatric studies/trials only: Pediatric population
- Geriatric population
- Lactating/nursing mothers
- Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- Orphan or rare disease population
- Pregnant women
- Racial/ethnic population
- Not applicable

3. (Complete if applicable) Additional comments about the PMR/PMC (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 “core” milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements⁸

1. The PMR/PMC is clear, feasible, and appropriate⁹ because: *[Select all that apply]*

- The study/clinical trial meets criteria for a PMR or a PMC.
- The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- The applicant has adequately justified the choice of milestone dates.
- The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. (If the PMR/PMC is a randomized controlled clinical trial) The following ethical considerations were made with regard to:

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug’s efficacy or safety.

⁸ This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division’s Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

⁹ See POLICY section of CDER MAPP 6010.9.

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

3. **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.**

Insert electronic signature (usually the Deputy Director for Safety)

APPEARS THIS WAY ON ORIGINAL

Appendix A PMR/PMC Development Template (FRM-ADMIN-60)

Instructions for Use

[click [here](#) to return to the template]

Purpose:

The PMR/PMC Development template (hereafter, template) is a review tool to help the team decide that PMRs/PMCs are needed, articulate the rationale for the PMRs/PMCs, obtain initial supervisory concurrence, and to inform discussions with the applicant.

Who completes this template:

The **PMR/PMC Development Coordinator** (usually the OND division's Deputy Director for Safety) may delegate the initial draft (i.e., filling out) of the template to an **assigned reviewer**. However, the PMR/PMC Development Coordinator is responsible for ensuring the accuracy and completeness of the template and for signing off on the template.

How to complete this template:

The assigned reviewer and PMR/PMC Development Coordinator should complete the template by following the *Instructions For Use*. The PMR/PMC Development Coordinator will review each PMR/PMC to ensure it is clearly written, has an appropriate rationale, and that milestones were appropriately selected to result in timely submission of appropriate data to address the issue that prompted the PMR/PMC.

A separate template is completed for **each** individual PMR and 506B “reportable” PMC.¹⁰ The separate templates are then combined into one document for archiving (see “How to archive the completed template”).

A draft template should be completed by the date targeted to begin PMR/PMC discussions with the applicant, as documented in the Filing Letter. Once concurrence on the PMR/PMC is reached with the applicant, the draft language in the template can be finalized.

How to archive the completed template:

The OND division's Safety Regulatory Project Manager should ensure appropriate sign-off on the completed template, as determined by the division, and that the process below is followed to ensure the completed template is filed correctly.

Completed templates for all PMRs and 506B “reportable” PMCs for a specific application should be combined and filed in CDER's electronic archival system as a single document.¹¹ This single document should be filed as *PMR/PMC Development Template* before filing the action letter that establishes the PMR(s)/PMC(s).

For (s)NDA/(s)BLA submissions, the completed, signed template should be included in the Action Package.

¹⁰ 506B “reportable” includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 “reportable.” A separate development template is used for 506 B *non-reportable* (e.g., chemistry, manufacturing, and controls (CMC)) PMCs.

¹¹ A single document facilitates data entry by the document room by preventing the need to upload and archive multiple templates.

Instructions:

SECTION A: Administrative Information [Click [here](#) to return to Section A of the template]

Complete each field in section A. Do not leave any fields blank.

SECTION B: PMR/PMC Information [Click [here](#) to return to Section B of the template]

- 1. PMR/PMC Description:** In the textbox, enter the wording for the PMR/PMC that will go in the letter notifying the applicant of the PMR/PMC (e.g., NDA action letter) and will also display in the FDA’s PMR/PMC database. The PMR/PMC description should be written clearly enough to result in the applicant’s timely submission of the appropriate data to address the issue that prompted the postmarketing study or clinical trial.

PMR/PMC descriptions are specific to the drug, indication, and issues under evaluation. Nevertheless, PMR/PMC descriptions should generally reflect the design of the clinical trial or study (e.g. randomized, double-blind, active control trial; registry based prospective cohort study), the population(s) to be studied, the exposure or intervention of interest, a comparator group (if applicable), and the study/trial goals and objectives.¹²

Avoid limiting the PMR/PMC description to a citation of the name of a specific study or clinical trial that may be ongoing (e.g., “Complete trial ABC123, *A Randomized, Placebo-Controlled Efficacy Trial of DRUG against COMPARATOR*”). The study/trial name may be included, but in addition, the PMR/PMC description should describe the design features of the study or clinical trial. In this way, should unforeseen developments preclude completion of the named study/trial, the PMR/PMC description provides sufficient information for FDA, the applicant, and the public to determine the type of study/trial that would be considered sufficient to fulfill the PMR/PMC.

Certain types of studies and clinical trials are commonly issued as PMRs/PMCs (e.g., drug-drug interaction trials; hepatic impairment PK trials). For these, a ‘standard’ PMR/PMC description may be employed [\[see Appendix B for examples\]](#).

- 2. PMR/PMC Milestones:** List the PMR/PMC milestones in the specified format.

Dates should be specified for all milestones. The milestone date format should be MM/YYYY; however, the milestone date format for PREA PMRs may be MM/DD/YYYY if a day is specified.

The Final Protocol Submission, Study/Trial Completion, and Final Report Submission milestones are considered “core” PMR/PMC milestones. These are included in every PMR/PMC schedule unless they are not applicable (e.g., study/trial is ongoing; the PMR is for a medical countermeasure study/trial that will not be initiated unless there is an emergency).

¹² The PMR/PMC description may also include primary and important secondary endpoints, as relevant. Typically the PMR/PMC description should not include description of milestones or other indicators of study/trial progress (e.g., frequency of interim reports), as these are described in the PMR/PMC timetable. .

The Draft Protocol Submission milestone may be included to ensure sufficient time for FDA review and comment on the protocol before it is finalized.¹³

“Other” milestones may include interim or annual report submission or subject accrual milestones.

Typically, submission of revised labeling (to reflect results from completed studies/trials are **not** included as PMR/PMC milestones.¹⁴

SECTION C: PMR/PMC Rationale [Click [here](#) to return to Section C of the template]

1. Describe the review issue and the goal of the study or clinical trial.

This section should summarize the **rationale** for the study/trial. The section should not repeat the description of the PMR/PMC provided in Section B.

The summary should briefly identify the review issue (safety signal for FDAAA PMRs; efficacy or other question for non-FDAAA PMRs), cite the source of the data if it includes information external to the application, and explain the intent of the study/trial and why we think the results of the PMR/PMC will be important.

The intent of the study/trial is the explanation of what it is that FDA wants to know. Intents include, but are not limited to:

- Signal detection (e.g., detecting potential serious risks associated with the drug)
- Signal refinement (e.g., checking to determine whether an identified safety signal persists; conducting surveillance to obtain additional follow-up on a known serious risk)
- Signal evaluation (e.g., obtaining a precise estimate of the serious risk associated with a drug)

Examples of a PMR/PMC rationale:

DRUG-X is metabolized through CYPYYYY, which can be inhibited by COMMONDRUGZ. This DDI trial will evaluate whether DRUGX levels are sufficiently increased to warrant a dose reduction when used concurrently with COMMONDRUGZ, to reduce the severity and/or likelihood of serious adverse effects caused by DRUGX.

DRUG-Y is intended for chronic use in patients with CONDITIONA. During clinical development of DRUG-Y, the maximum duration of patient exposure was 6 months. This long-term efficacy trial will evaluate whether positive treatment effects are maintained when exposures exceed 6 months.

¹³ “Final” implies that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the date for this milestone should be selected to allow for the discussion period needed to create a well-designed study or clinical trial. See FDA guidance for industry, [Postmarketing Studies and Clinical Trials — Implementation of Section 505\(o\)\(3\) of the Federal Food, Drug, and Cosmetic Act](#).

¹⁴ Exceptions are PREA and Accelerated Approval PMRs, since those authorities necessitate submission of revised labeling to reflect PMR results.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval.

This section documents the statutory or regulatory authorities that *necessitate* that the study or clinical trial be done post-approval (e.g., confirmatory trials for accelerated approval), **or** why the issue does not preclude an approval action and can be evaluated after approval without compromising safety and efficacy considerations.

Only one option should be selected.

3. For FDAAA PMRs and 506B PMCs only

This section expands on the reasons why the FDAAA PMR or 506B PMC can be conducted post-approval and do not need to be addressed prior to approval.

This section applies only to FDAAA PMRs and 506B “reportable” PMCs because the statutory and regulatory basis is sufficient explanation for all other PMRs (i.e., PREA, accelerated approval, and animal rule PMRs).

4. For FDAAA PMRs only

This section summarizes the statutory purpose of the FDAAA PMRs, the reasons why FAERS¹⁵ and Sentinel’s ARIA¹⁶ system are insufficient for this purpose and, as applicable, why a study is insufficient for this purpose and a clinical trial is necessary. FDA must make each of these hierarchical determinations before requiring a FDAAA PMR.

Question 4.a: identify the purpose of the study/clinical trial:

As mandated by Section 505(o)(3)(A), postmarketing studies and clinical trials may be required for the three purposes listed below. Therefore to document the rationale for requiring a FDAAA PMR, you must identify one of the following:

- To assess a known serious risk related to the use of the drug
- To assess signals of serious risk related to the use of the drug
- To identify an unexpected serious risk when available data indicates the potential for a serious risk

Questions 4.b-d: Explanation of whether FAERS and Sentinel’s postmarket ARIA system are sufficient for the purposes described in Q1. and Q4.a.

Studies/trials are required as FDAAA PMRs when FAERS and the ARIA system are determined to be insufficient to assess the safety issue. Responses to questions 4.b-d briefly summarize the reasons why FAERS and the ARIA system have been determined insufficient.

The explanation of why FAERS is insufficient to further characterize the serious risk(s) of concern should be informed by the FDA draft guidance, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* and by discussions with the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE).

The explanation of why the ARIA system is insufficient to further characterize the serious risk(s) of concern should be informed by discussions with the Division of Epidemiology (DEPI) in OSE, the DEPI *ARIA Sufficiency*

¹⁵ FDA Adverse Event Reporting System (FAERS)

¹⁶ Active Risk Identification and Analysis (ARIA)

Memorandum, and the aforementioned FDA guidance. It is acceptable to excerpt text from the *ARIA Sufficiency Memorandum*.

Question Q4.e: Determination of whether a study is sufficient for the purposes described in Q1. and Q4.a.

The explanation of why a study is (or is not) sufficient to further characterize the serious risk(s) of concern should be informed by the nature of the study (e.g., an animal study is the generally accepted standard for assessment of genotoxicity) and relevant discussions with other scientific disciplines such as Clinical Pharmacology, Pharmacology/Toxicology, and DEPI.

Examples of situations when an *observational* study may not be sufficient, and a clinical trial required, include (but are not limited to):

- Need to minimize bias and/or confounding via randomization
- Need for placebo control
- Need to capture detailed information about covariates or confounders that are either not routinely collected during the usual course of medical practice, or not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- Need pre-specified and prospective active data collection of outcome(s)/endpoint(s)

Question Q4.f: Conclusion that only a clinical trial is sufficient for the purposes described in Q1. and Q4.a.

Under FDAAA, when FAERS, the ARIA system, and a study are considered insufficient, then a clinical trial is necessary for the specified purposes.

5. For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal?

This section should be completed for all PMRs and PMCs.

Select the best summary description of the type of postmarketing study or clinical trial. Select only **ONE** option under either “type of study” or “type of clinical trial.” Do not choose a option under both categories.

SECTION D: PMR/PMC Additional information [Click [here](#) to return to Section D of the template]

This section provides additional information about the PMRs and PMCs.

1. Does this PMR/PMC apply to other drugs (e.g. drugs in a therapeutic class)?

Select “yes” if the PMR/PMC will apply to other drugs in the same therapeutic class or different formulations of the same drug.

2. This study or clinical trial focuses on the following special population or circumstances:

Select the appropriate box(es) if the study or trial focuses on a special population. If not, select “not applicable.”

3. (Complete if applicable) Additional comments about the PMR/PMC.

Complete this text box only if there are additional comments to add about this PMR or PMC (e.g., points or concerns not previously described; explanation for inclusion of additional milestones besides the 3 “core” milestones).

Note: Additional milestones also must be tracked by the division (see [MAPP 6010.2](#), *Responsibilities for Tracking and Communicating the Status of Postmarketing Requirements and Commitments*).

If nothing additional to add, leave text box blank.

SECTION E: PMR/PMC Development Coordinator Statements [Click [here](#) to return to Section E of the template]

This section is completed only by the the PMR/PMC Development Coordinator (usually the OND division's Deputy Director for Safety) who will sign off on the completed Development Template.

1. The PMR/PMC is clear, feasible, and appropriate because (select all that apply):

Select the considerations FDA made to determine that the study or clinical trial is feasible to conduct, appropriately described, and informed by discussions with the applicant.

2. The following ethical considerations were made with regard to randomized, controlled, clinical trials:

This section is only completed if the PMR/PMC is for a randomized, controlled, clinical trial, including a clinical pharmacology trial.

It is necessary to provide this information in order to demonstrate that the relevant ethical considerations have been made regarding the trial, as recommended to FDA in the Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*.

3. This PMR/PMC has been reviewed for clarity and consistency... reliability of drug quality.

This attestation is to document that the necessary considerations have been made regarding the need for and appropriateness of the postmarketing study or clinical trial.

APPENDIX B

Examples of Standard Descriptions for Certain Clinical Pharmacology PMRs and PMCs

1. Examples of standard language for Clinical Pharmacology PMRs

- Renal Impairment
Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
- Hepatic Impairment
Conduct a clinical pharmacokinetic trial to determine an appropriate dose of DRUG to minimize toxicity in patients with hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
- Drug-Drug Interactions-victim drug (CYP inhibitors, UGT or transporter)
Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP (or other enzyme/transporter) #X# inhibitor on the single dose pharmacokinetics of DRUG to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”
- Drug-Drug Interactions-perpetrator drug as inhibitors of CYP#X#
Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of DRUG on the single dose pharmacokinetics of XYZ drug (a sensitive CYP#X# substrate) to address the potential for excessive drug toxicity. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

2. Examples of standard language for Clinical Pharmacology PMCs

PMCs to assess for potential decreased drug exposure, with potential loss of efficacy.

- Drug-Drug Interactions (gastric acid reducing agents)
Conduct a clinical pharmacokinetic trial to evaluate if gastric acid reducing agents (proton pump inhibitors, H2-receptor antagonists, and antacids) alter the bioavailability of DRUG and to determine appropriate dosing recommendations for DRUG with regard to use of concomitant gastric acid reducing agents.
- Drug-Drug Interactions-Induction
Conduct a clinical pharmacokinetic trial with repeat doses of a CYP#X# inducer on the single dose pharmacokinetics of DRUG to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”
- Anti-Drug Antibody Responses
Conduct an assessment of binding and neutralizing anti-drug antibody (ADA) responses with a validated assay (requested in PMC X) capable of sensitively detecting ADA responses in the presence of DRUG levels that are expected to be present in the serum at the time of patient sampling. The ADA response will be evaluated in at least ### DRUG-treated patients. The final report will include information on the level of DRUG in each patient’s test sample at each sampling point.

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# 761070 Benralizumab
Product Name:

PMC #1 Description: Perform a leachable study to evaluate the (b) (4) drug product container closure systems through the end of shelf-life when stored under the recommended conditions. Perform testing at regular intervals and include appropriate methods to detect, identify, and quantify organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Update study results in the BLA Annual Report. Submit the complete data and risk evaluation for potential impact of leachables on product safety and quality to the BLA.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission (Drug Product):	<u>12/31/2023</u>
	Other: <u>Bulk Product Report Submission</u>	<u>12/31/2021</u>

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

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

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

The results from the extractables and leachables studies that have been performed and the clinical and product stability studies indicate that the presence of leachates from the (b) (4) commercial container closure systems is not a significant safety or product quality issue. However, comprehensive real-time leachable studies through the end of (b) (4) drug product expiry periods were not performed.

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

3. Forced extraction and real-time leachables studies for (b) (4) drug product container closure systems (b) (4) in its commercial formulation, and a justification was not provided. A comprehensive real-time study of all potential leachables should be performed using (b) (4) drug product in their respective container closure systems through the end of shelf-life. These studies should include methods to detect volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals. Each of these types of potential leachables should be assessed to enable a risk evaluation of potential impact to safety and product quality.

4. [OMIT – for PMRs only]

5. 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 leachable studies using the (b) (4) drug product container closure systems using methods to detect, identify, and quantify organic non-volatile compounds, volatile compounds, semi-volatile compounds, and metal species and evaluate the impact of leachables to product safety and quality.

6. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?

- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

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

/s/

SALLY M SEYMOUR
10/30/2017

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Date	August 25, 2017
To	Kelly Ballard, RPM and Jennifer Swisher, lead Reviewer CDER/OPQ/OBP
Requesting Division	CDER/OPQ/OBP
From	Kathleen Fitzgerald CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Alan Stevens, Branch Chief CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for Submission # BLA 761070 ICCR2017-00399 ICC1700014
Recommendation	The BLA application, applicant IR responses and the device constituent parts related DMFs have provided adequate container closure system information and acceptable functional performance test reports. The consulting reviewer has determined that the device constituent parts of the combination product have been designed appropriately for the product's intended use and essential performance requirements.

Digital Signature Concurrence Table	
Reviewer	<p>Kathleen E. Fitzgerald -A</p> <p>Digitally signed by Kathleen E. Fitzgerald -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093027, cn=Kathleen E. Fitzgerald -A Date: 2017.08.25 12:50:51 -04'00'</p>
Team Lead	
Branch Chief	<p>Alan M. Stevens -S</p> <p>Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2017.09.01 08:34:58 -04'00'</p>

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Table 1. Submission Information	
ICCR # (Lead)	ICCR2017-00399
ICCR SharePoint Link	http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/Item/displayifs.aspx?List=337aa2e9%2D7692%2D4a76%2Dada9%2Dae967ad4a69b&ID=564&Web=703664f2%2D33ef%2D4c9f%2Da6f2%2De1f658e187f9
ICC tracking # (Lead)	ICC1700014
Submission Number	BLA761070
Sponsor	AstraZeneca AB
Drug/Biologic	Benralizumab
Indications for Use	Benralizumab is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody indicated as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype.
Device Constituent	Prefilled syringe and needle shield
Related Files	

Table 2. Review Team	
CDER/CBER Lead Review Division	Jennifer Swisher
Submission RPM	Kelly Ballard
Lead Device Reviewer	Kathleen Fitzgerald
The CDRH review is being managed under ICC #: ICC170014	

Table 3. Important Dates		
Interim Due Dates	Meeting Date	Due Date
Filing	1-15-2017	
74-Day Letter		
Mid-Cycle	4-27-2017	
Primary Review		7-21-2017

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2. PURPOSE/BACKGROUND

2.1. Scope

CDER's request: Benralizumab is supplied at 30 mg in 1.0 mL solution for subcutaneous injection in a prefilled syringe. CDRH has been consulted to review the PFS container closure system.

CDER will be reviewing of all the drug contacting parts of the container closure system.

2.2. Prior Interactions

None

2.2.1. Related Files

2.3. Indications for Use

Combination Product	Indications for Use
Benralizumab	Is an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody indicated as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype.
(b) (4) Syringe 1ml	Administration of medication.

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Date - Version	Location
ICC1700014		CTS
ICCR2017-00399		Sharepoint
BLA 761070		Global submit
DMF (b) (4)		
DMF- (b) (4)		
(b) (4)		(b) (4)

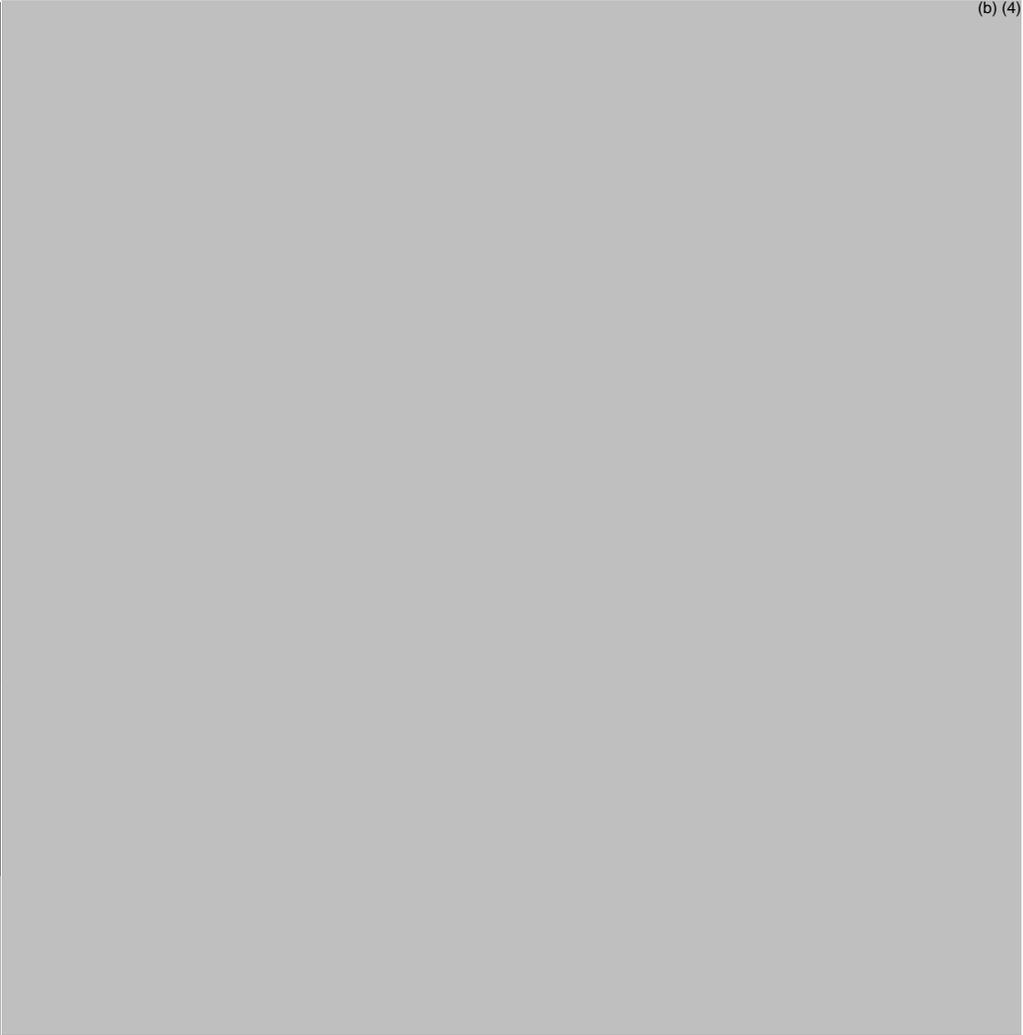
Table 1.4.2-1 List of Files Incorporated by Reference in Module 3

BLA Section	Name of File	Reference Number	Referenced Information
	Type V Facilities Drug Master File:		

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3.2.S.2.1 3.2.S.2.5 3.2.P.3.1 3.2.A.1	
3.2.S.2.5 3.2.P.3.1 3.2.P.3.5 3.2.A.1	
3.2.P.7 3.2.R	
3.2.P.7 3.2.R	
3.2.P.7 3.2.R	
3.2.R	

4. DEVICE D

Container Closure System Description from P.2.4.2.1 in BLA761070

The prefilled syringe is the intended commercial presentation and was developed for dose administration convenience. The prefilled syringe primary packaging  (b) (4)

 (b) (4)
The primary packaging  (b) (4)

 (b) (4) The secondary packaging includes a unit tray and lid stock  (b) (4), an opaque paperboard unit carton to protect the Drug Product from light  (b) (4) and package inserts.

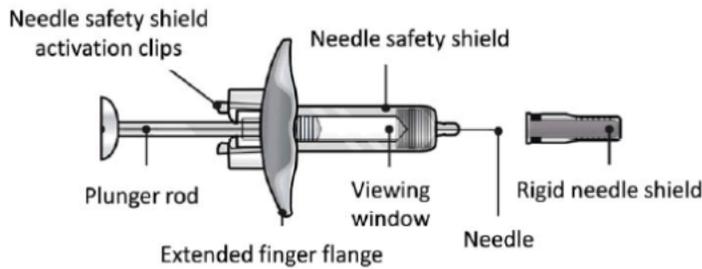
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The primary packaging components for the prefilled syringe (b) (4) 1 mL long syringe] were unchanged between Process 3 Clinical and Process 3 Commercial. The syringe barrel is manufactured from USP/Ph. Eur./JP Type I (b) (4) glass (b) (4). A stainless steel 29-gauge, 1/2-inch (b) (4) needle (b) (4). The needle is covered with a rigid needle shield composed of a (b) (4) elastomeric needle shield (in contact with the needle), which has a rigid (b) (4) outer cap. The (b) (4) elastomeric needle shield complies with USP/Ph. Eur. requirements. The rigid needle shield (b) (4). The plunger stopper is composed of a (b) (4) elastomer that complies with USP/Ph. Eur./JP requirements (b) (4).



Section R of the application contained the following container closure system information:



Figure R.2.4-2 Accessorized Prefilled Syringe (APFS)

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R.2.3 Intended Use

Benralizumab is intended for the treatment of patients with [REDACTED] (b) (4)

Benralizumab is intended for [REDACTED] (b) (4) with a frequency of every 4 weeks for the first 3 doses followed by every 8 weeks thereafter through subcutaneous injections.

R.2.3.1 Intended Users

Benralizumab is administered by health care professionals (HCPs). HCPs are assumed to have injection experience. HCPs are expected to be familiar with subcutaneous injection procedures and good hygiene and injection practices. HCPs are not expected to have any dexterity or sensory deficiencies beyond what is expected in the broader population.

[REDACTED] (b) (4)

R.2.3.2 Intended Use Environments

HCPs are expected to administer benralizumab in a clinical environment.

R.2.3.3 Training [REDACTED] (b) (4)

Any HCP intending to administer benralizumab [REDACTED] (b) (4)
[REDACTED] (b) (4)

R.2.4 General Description and Principles of Operation

The APFS is a single use, disposable system that is designed to administer the labeled dose of benralizumab to the subcutaneous space during one injection and automatically provide a safety mechanism to reduce the occurrence of accidental needle sticks during disposal of the system. Administration of benralizumab by a HCP using the APFS [REDACTED] (b) (4)

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Table R.2.6-1 Description of Device Components

Component	Description	Supplier
Prefilled Syringe	1 mL long Type I glass syringe barrel with (b) (4) (b) (4) 29 gauge (b) (4) 1/2" needle, rigid needle shield (b) (4)	(b) (4)
Plunger Stopper	1 mL long plunger stopper, (b) (4) (b) (4) elastomer (b) (4)	
Needle Safety Shield	(b) (4) needle guard, (b) (4) body and guard with (b) (4)	
Plunger Rod	(b) (4) needle guard plunger rod, (AstraZeneca logo) blue (b) (4)	
Extended Finger Flange	(b) (4) finger flange, white (b) (4)	

CDRH Reviewer’s Comments: The Applicant has provided an adequate description of the container closure system for its intended use and method of operation. The combination product is to be administered by a health care professional in a clinical setting. Based on the device components descriptions and method of operation it appears to be an adequate container closure system for BLA761070.

5. DESIGN CONTROL REVIEW

5.1. Design Review Summary

Table R.2.7.1-1 Critical Performance Specifications

Specification	Description	
Break-loose force	Force required to initiate the injection	(b) (4)
Glide force	Force to sustain injection	
RNS pull-off force	Force to remove needle shield from syringe barre	
Flange breakage resistance	Force to deform or break syringe barrel flange	
Needle separation force	Force to remove needle from syringe barre	
Needle patency	Needle diameter confirmation	
Delivered volume	Fluid volume confirmation during injectio	
Needle length	Length of staked needle protruding from syringe barrel	
Resistance to override	Force to overcome safety feature of device	

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Indication of injection stroke completion	Indication by visual means that the injection stroke has been completed	(b) (4)
Visual differentiation between "ready to deliver" and "delivered"	The state of the APFS, when ready to deliver a dose, shall be visually different from its state when the dose has been delivered	

Table R.2.7.1-1 Critical Performance Specifications

Specification	Description	
Indication of safe mode	It is apparent as to when the device is in safe mode	(b) (4)

Table R.2.7.1-2 Component Shelf-Life

Component	Supplier	Est	-Life
Prefilled Syringe	(b) (4)		(b) (4)
Plunger Stopper			
Needle Safety Shield			
Plunger Rod			
Extended Finger Flange			

The stability testing for functional device attributes of the APFS include break-loose and glide forces, and delivered volume. These stability data

as RNS removal force, Section P.8.3.

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Table R.6.1-1 Biological Evaluation

Component	Classification	List of Tests	BD Statements
Rigid needle shield	Nature of body contact: External communicating devices; Blood path indirect Duration of contact: Limited exposure < 24 hours	USP <87>, <88> Cytotoxicity, haemocompatibility, acute systemic toxicity, intracutaneous reactivity, sensitization and pyrogenicity	Rigid Needle Shield Biocompatibility Statement and Summary
Plunger stopper	Nature of body contact: External communicating devices; Blood path indirect Duration of contact: Limited exposure < 24 hours	USP <87>, <88> Cytotoxicity, haemocompatibility, acute systemic toxicity, intracutaneous reactivity, sensitization and pyrogenicity	(b) (4) Biocompatibility/ Toxicology Summary
Syringe barrel needle. (b) (4)	Nature of body contact: External communicating devices; Blood path indirect Duration of contact: Limited exposure < 24 hours	USP <87> and <88> Cytotoxicity, haemocompatibility, acute systemic toxicity, intracutaneous reactivity, sensitization and pyrogenicity	Glass Barrel Biocompatibility/ Toxicology Summary
(b) (4) (Needle safety shield, Plunger rod and Extended finger flange)	Body contact: Surface Devices - Skin Duration of contact: Limited exposure < 24 hours	Cytotoxicity, intracutaneous reactivity and sensitization	(b) (4) ISO 10993 Compliance Statement; (b) (4) Blue Plunger Rod ISO 10993 Compliance Statement; (b) (4) White Finger Flange ISO 10993 Compliance Statement

5.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		Section 3.2.R Accessorized Prefilled Syringe, Section R.2.7 Device Design Requirements
Design Verification Data included	X		Section 3.2.R Accessorized Prefilled Syringe,

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in the NDA / BLA or adequately cross-referenced to a master file.			Section R.8 Design Verification
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		Section 3.2.R Accessorized Prefilled Syringe, Section R.7 Risk Management Module 2, 2.5.6 Benefits and Risks Conclusions
Validation Data <ul style="list-style-type: none"> Human factors Clinical data 	X		Section 3.2.R Accessorized Prefilled Syringe, Section R.9 Human Factors Engineering
	X		Section R.10.2 Actual Use Clinical Studies
Traceability Documentation	X		

5.1.2. Design Control Review

6. DESIGN VERIFICATION AND VALIDATION REVIEW

6.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		X			X	
Biocompatibility		X			X	
Sterility		X			X	
Software / Cybersecurity			X			
Electrical Safety / EMC			X			
Human Factors		X			X	

*Other discipline specific consults may be necessary based on product characteristics

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Table R.1.2.4-1 Standards and Guidances Used for APFS Presentation

Standard/ Regulation	Title/ Description
2005 FDA Guidance	Medical Devices with Sharps Injury Prevention Features (b) (4)
ASTM D4169-14	Standard Practice for Performance Testing of Shipping Containers and Systems
ASTM D6653-13	Standard Test Methods for Determining the Effects of High Altitude on Packaging Systems by Vacuum Method
DIN 13097	Hypodermic Needles – Part 4: Point geometry, requirements, and testing (b) (4)
ISO 10993	Biological evaluation of medical devices
ISO 11040	Prefilled Syringes (b) (4)
ISO 11608	Needle-based injection systems for medical use
ISO 23908	Sharps injury protection (b) (4)
ISO 8871	Elastomeric parts for parenterals and for devices for pharmaceutical use (b) (4)
ISTA 3A	International Safe Transit – Packaged products for Parcel Delivery System Shipment 70 kg or less
ISTA 3B	Packaged products for less-than-truckload (LTL) shipment
Ph.Eur. 0520	Parenteral Preparations (b) (4)
Ph.Eur. 2.6.14	Bacterial Endotoxins
Ph.Eur. 2.9.17	Test for Extractable Volume of Parenteral Preparations
Ph.Eur. 2031	Monoclonal Antibodies for Human Use (b) (4)
Ph.Eur. 3.2	Containers, The container does not interact physically or chemically with the contents in a way that alters their quality beyond the limits tolerated by official requirements
Ph.Eur. 3.2.1	Glass Containers for Pharmaceutical Use
Ph.Eur. 3.2.9	Rubber Closures for Containers for Aqueous Parenteral Preparations
USP <1>	Injections
USP <381>	Elastomeric Closures for Injections
USP <660>	Containers – Glass
USP <71>	Sterility Tests
USP <85>	Bacterial Endotoxins Test
USP <1031>	The Biocompatibility of materials used in Drug Containers, Medical Devices and Implants
USP <1211>	Sterilization and Sterility of Compendial Articles
USP <87>	Biological reactivity tests, in vitro
USP <88>	Biological reactivity tests, in vivo. Acute toxicity/ Intracutaneous reactivity

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USP <87>	Biological reactivity tests, in vitro
USP <88>	Biological reactivity tests, in vivo - Acute toxicity/ Intracutaneous reactivity

Standard/ Regulation	Title/ Description
	(b) (4)
USP <151>	Pyrogen Test
USP <1663>	Assessment of Extractables associated with Pharmaceutical Packaging/ Delivery Systems
USP <1664>	Assessment of Drug Product Leachables associated with Pharmaceutical Packaging Delivery Systems

6.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase III Study utilized the to-be-marketed device	X		
Bioequivalence Study utilized to-be-marketed device	X		
Simulated Actual Use Study utilized to-be-marketed device	X		

The primary packaging components for the prefilled syringe (b) (4) 1 mL long syringe] were unchanged between Process 3 Clinical and Process 3 Commercial.

(b) (4)

Performing human factors activities supported the development of an PFS that meets the user needs and is free from unacceptable risk of use error. However, given the common and well understood use of PFSs by HCPs, it was determined by the Sponsor that data generated within the human factors engineering studies for (b) (4) HCP (b) (4) was not necessary to validate the product design.

6.3. Design Verification Review

Functionality/Performance Studies at Different Use Temperatures

The APFS was tested for functionality/performance when operated under normal use conditions (18-28!C room temperatures) and under foreseeable misuse conditions (2-8!C).

A sample size of N=29 was used for each of the use conditions, which provided 95% confidence and 90% reliability. For testing at room temperature, the samples were equilibrated for at least 30 minutes to room temperature prior to testing. For testing at 2-8!C, the samples were taken out of the cold storage unit one-by-one as the testing progressed and each sample was exposed to room temperature conditions for approximately 1 minute to ensure samples remained in the 2-8!C range. Table R.8.2.2-1 shows the results of the performance testing for the room temperature condition.

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Table R.8.2.1-1 Results of Functionality Tests after Shipping Pre- Conditioning

Sample Size = 29	Maximum Break-loose Force	Maximum Glide Force	RNS Pull-off Force Range	Minimum Force to Override Safety Mechanism
Results	8.9 N	6.6 N	9.3 – 13.7 N	98 N
Acceptance criteria	(b) (4) N	(b) (4) N	(b) (4) N	(b) (4) N
Pass/Fail	Pass	Pass	Pass	Pass

F = force; N = newtons; RNS = rigid needle shield

Table R.8.2.2-1 Results of Performance Tests at Room Temperature

Sample Size = 29	Maximum Break-loose Force	Maximum Glide Force	RNS Pull-off Force Range	Minimum Force to Override Safety Mechanism	Delivered Dose Volume
Results	8.5 N	7.1 N	8.9 – 16.7 N	110 N	1.0 mL
Acceptance criteria	(b) (4) N	(b) (4) N	(b) (4) N	(b) (4) N	(b) (4) mL
Pass/Fail	Pass	Pass	Pass	Pass	Pass

F = force; N = newtons; RNS = rigid needle shield

All N=29 devices that were tested at the cold temperature condition also maintained functionality. The needle safety shield was triggered and deployed at the end of dose for each of these samples.

R.9.1 Human Factors Engineering Approach/Requirements

(b) (4)

Performing human factors activities supported the development of an APFS that meets the user needs and is free from unacceptable risk of use error. However, given the common and well understood use of APFSs by HCPs, it was determined that data generated within the human factors engineering studies for (b) (4) HCP (b) (4) (b) (4) was not necessary to validate the product design. This position is in agreement with the Agency’s draft guidance document, “*Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*”.

R.9.2 Usability Studies

The use of the APFS by HCPs is considered validated through the successful completion of the clinical studies, the satisfaction of user requirements, and the determination that all risks associated with the device were reduced to acceptable levels. The existing human factors engineering studies that were conducted to support use by (b) (4) HCPs (b) (4) are summarized in the sections below as they are considered supportive of the conclusion that the APFS is able to be used safely and effectively by HCPs.

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Reviewer Comments: The Sponsor has provided adequate device constituent part and container closure system data and functional performance test results to demonstrate that the combination product will function/drug delivery as intended.

There was one IR regarding the sharps injury prevention feature and the Sponsor provided an adequate response. Please see at the end of the memo.

7. RISK ANALYSIS

7.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

7.2. Summary of Risk Analysis

R.7.1 Risk Management Overview

AstraZeneca has developed and implemented a risk management program to ensure compliance with the requirements of the AstraZeneca device development quality management system, ISO14971:2007 “*Medical Devices – Application of Risk Management to Medical Devices*”, and ICH Q9 “*Quality Risk Management*”. This risk management program covers the lifecycle of the finished product from design/development through postproduction until discontinuation from market. A risk management plan (RMP) was developed for the APFS presentation, which includes the process of estimating, evaluating and controlling risks, and the methodology for conducting user, design and process risk assessments.

R.7.2 Risk Management Summary

The RMP was followed to assess the risks associated with the APFS presentation. Risk analyses were conducted to cover the device design, production and end user risks. (b) (4)

(b) (4)
(b) (4) Table R.7.2-1 details the risk analyses performed.

Table R.7.2-1 Risk Management Performed for Benralizumab APFS Risk Management Activity Prepared By

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DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

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Table R.7.2-1 Risk Management Performed for Benralizumab APFS

Risk Management Activity	Prepared By
APFS Risk Management Plan	AstraZeneca
APFS Device Hazard Assessment	
APFS User Risk Assessment	
Design Risk Assessment of the Overall APFS Design (b) (4)	
Component Design, User and Manufacturing/Assembly Risk Management Activities	(b) (4)
Manufacture/Assembly Risk Analysis of the Final Assembly and Fill/Finish Process	

APFS = accessorized prefilled syringe

The risk assessments followed a failure modes, effects, and criticality analysis (FMECA) methodology for internal risk analysis. Individual FMECAs were prepared for the following areas of risk: design risks, process risks, and user risks. Table R.7.2-2 provides a description of these risk areas.

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Table R.7.2-2 Risk Management Areas Analyzed

Risk Area	Description
User	Evaluation of the intended use and foreseeable misuse of the drug delivery system
Design	Evaluation of the components/design elements/assemblies and ensure that any areas that might affect the safety of the drug delivery system are considered
Process	Evaluation of the supply chain from manufacture of components final assembly, packing and release to the supply chain (b) (4)

These risk management activities were used to identify the known risks associated with the benralizumab APFS. Following risk identification, the risks were analyzed and evaluated for acceptability. This evaluation was determined by assigning an appropriate severity level and occurrence level to each identified risk.

Table R.7.2-3 and Table R.7.2-4 detail the definitions of severity level and occurrence level, respectively, used by AstraZeneca. Once each risk was identified and assigned a severity level and an occurrence level, a risk category was determined based on the severity and occurrence levels.

The risk category was then used to determine the level of action required. Table R.7.2-5 provides the actions required based on the risk category.

Table R.7.2-3 Severity Definitions

Category	1 Negligible	2 Minor	3 Serious	4 Critical	5 Catastrophic
Effect on User Patient	Inconvenience or temporary discomfort	Results in reversible, non-threatening injury or temporary impairment not requiring professional medical intervention	Results in reversible, non-life threatening injury or temporary impairment requiring professional medical intervention	Results in permanent (irreversible) injury or impairment or life-threatening injury	Results in death

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Table R.7.2-4 Probability of Occurrence Definitions

Category	1 Improbable	2 Remote	3 Occasional	4 Probable	5 Frequent
Probability Estimate	< 1/1,000,000	≥ 1/1,000,000 < 1/100,000	≥ 1/100,000 < 1/10,000	≥ 1/10,000 < 1/1,000	≥ 1/1,000
Description	Unlikely to occur (Equal to six sigma and assurance level of terminal sterilization)	Not expected to result in any lot failures, but may result in a very small number of field reports	Will result in very few lot failures and minimal field reports	Will result in some lot failures and/or regular field reports	Likely to affect every lot or batch and will be consistently experienced by users

Table R.7.2-5 Risk Category Definitions

Risk Category	Definition	Comment / Action
Low	Insignificant	Risk can be considered insignificant. The risk can be considered to be controlled and no additional risk control measures are required
Medium	Investigate Further	Further risk control measures should be considered to reduce this risk to its lowest level. Risks are accepted by approval of the Risk Summary report. All risk control options will be considered unless the risk controls will not reduce risks further, or the risk controls are incompatible with other risk controls
High	Unacceptable	Risks not acceptable and action must be taken to reduce the risk. If no further risk reduction measures are feasible, data shall be gathered and reviewed to determine whether the medical benefits outweigh the residual risk

R.7.2.1 Design Risk Assessment Results

The design risk assessment identified the potential design risks associated with the benralizumab APFS. There were no risks identified in the high risk category. Risks that were identified as medium were reduced to acceptable levels or justified as acceptable.

R.7.2.2 User Risk Assessment Results

The user risk assessment identified the potential user risks associated with the benralizumab APFS. There were no risks identified in the high risk category. Risks that were identified as medium were reduced to acceptable levels or justified as acceptable.

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**FULL PRESCRIBING INFORMATION****1 INDICATIONS AND USAGE**

FASENRA is indicated for the add-on maintenance treatment for patients with severe asthma aged ^(b)(4) years and older, and with an eosinophilic phenotype [see [ClinicalStudies\(14\)](#)].

Limitations of use:

- FASENRA is not indicated for treatment of other eosinophilic conditions.
- FASENRA is not indicated for the relief of acute bronchospasm or status asthmaticus.

2 DOSAGE AND ADMINISTRATION**2.1 Recommended Dose**

FASENRA is for subcutaneous use only.

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The recommended dose of FASENRA is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection into the upper arm, thigh, or abdomen. (b) (4)

(b) (4)

2.2 Preparation and Administration

FASENRA should be administered by a healthcare professional. In line with clinical practice, monitoring of patients after administration of biologic agents is recommended [see [Warnings and Precautions \(5.1\)](#)].

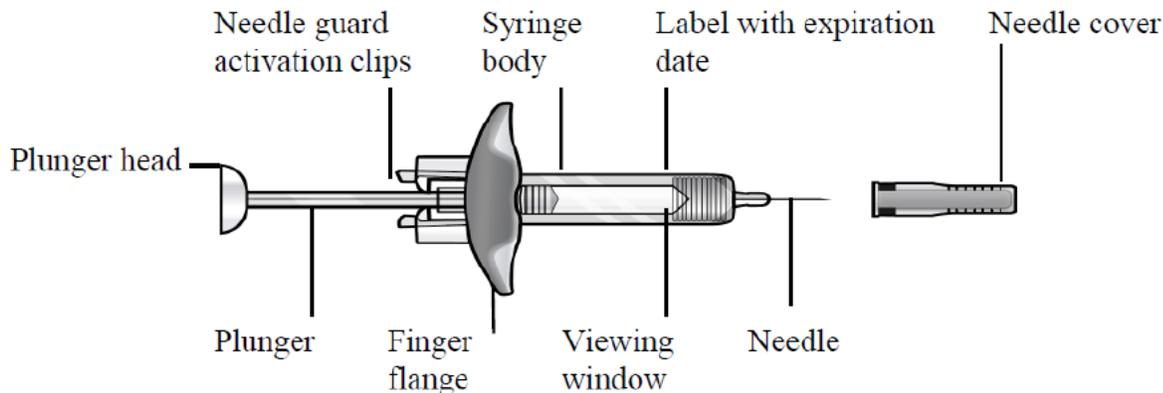
Prior to administration, warm FASENRA by leaving carton at room temperature (b) (4) 30 minutes. Administer FASENRA within 24 hours or discard into sharps container.

Instructions for Prefilled Syringe with Needle Safety Guard

Refer to [Figure 1](#) to identify the prefilled syringe components for use in the administration steps.

Figure 1

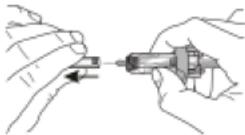
Figure 1



Do not touch the needle guard activation clips to prevent premature activation of the needle safety guard.

1 **Grasp the syringe body**, not the plunger, to remove prefilled syringe from the tray. Check the expiration date on the syringe. Visually inspect FASENRA for particulate matter and discoloration prior to administration. FASENRA is clear to opalescent, colorless to slightly yellow, and may contain translucent or white to off-white particles. Do not use FASENRA if liquid is cloudy, discolored, or if it contains large particles or foreign particulate matter. The syringe may contain a small air bubble; this is normal. **Do not** expel the air bubble prior to administration.

2



Do not remove needle cover until ready to inject. Hold the syringe body and remove the needle cover by pulling straight off. Do not hold the plunger or plunger head while removing the needle cover or the plunger may move. If prefilled syringe is damaged or contaminated (for example, dropped without needle cover in place), discard and use a new prefilled syringe.

3



Gently pinch the skin and insert the needle at the recommended injection site (i.e., upper arm, thigh, or abdomen).

4



Inject all of the medication by pushing in the plunger all the way until the plunger head is **completely between** the needle guard activation clips. **This is necessary to activate the needle guard.**

5



After injection, maintain pressure on the plunger head and remove the needle from the skin. Release pressure on the plunger head to allow the needle guard to cover the needle. **Do not re-cap the prefilled syringe.**

6

Discard the used syringe into a sharps container.

3 DOSAGE FORMS AND STRENGTHS

Injection: 30 mg/mL solution of FASENRA in a single-dose prefilled syringe. FASENRA is a clear to opalescent, colorless to slightly yellow solution and may contain translucent or white to off-white particles.

4 CONTRAINDICATIONS

FASENRA is contraindicated in patients

5 WARNINGS AND PRECAUTIONS

- **Hypersensitivity Reactions**

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, urticaria, rash) have occurred following administration of FASENRA. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, FASENRA should be discontinued [[see Contraindications\(4\)](#)].

- **Acute Asthma Symptoms or Deteriorating Disease**

FASENRA should not be used to treat acute symptoms or acute exacerbations. Do not use FASENRA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment.

- **Reduction of Corticosteroid Dosage**

Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with FASENRA. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

• **Parasitic (Helminth) Infection**

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known helminth infections were excluded from participation in clinical trials. It is unknown if FASENRA will influence a patient's response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with FASENRA. If patients become infected while receiving treatment with FASENRA and do not respond to anti-helminth treatment, discontinue treatment with FASENRA until infection resolves.

6 ADVERSE REACTIONS

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity Reactions [see [Warnings and Precautions\(5.1\)](#)]

9. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

Release testing was completed on the combination product. A summary and conclusion were provided in section P.8.1 of the application.

P.8.1.2.1 Overview of Stability Program

Stability studies on primary and commitment lots were conducted to establish Drug Product shelf life at the long-term storage condition of 2-8°C. The Drug Product uses a prefilled syringe (b) (4) (PFS (b) (4)) as the primary container closure system, described in [Section P.2.4](#).

All primary and commitment Drug Product stability studies were performed with benralizumab material in the commercial formulation (20 mM histidine/histidine-HCl, 0.25 M trehalose dihydrate, 0.006% (w/v) polysorbate 20, pH (b) (4) and in the same primary container closure.

Drug Product commitment lot stability studies were performed using process validation lots at the commercial formulation concentration (30 mg/mL) and evaluated under conditions representative of recommended commercial long-term storage conditions. Drug Product process validation lots 020F15, 021F15, and 004K15 are the commitment lots for the 30 mg dose.

Drug Product primary lot stability studies include three clinical lots at the commercial concentration (30 mg/mL) and two representative bracketing lots ((b) (4) mg/mL and (b) (4) mg/mL). Drug Product primary lots were derived from Drug Substance produced at commercial site (MedImmune LLC Frederick Manufacturing Center; FMC) at scale and were filled at the commercial Drug Product manufacturing site (b) (4) Drug Product primary lots are the following: Process 3 Clinical lots formulated at 30 mg/mL: lots 026A13, 002C14 and 001L14; and Process 3 Clinical lots: 004I12 (20 mg/mL) and 005I12 (50 mg/mL) which bracket the clinical and commercial dose. The results of the Drug Product comparability testing demonstrate that Process 3 Clinical and Process 3 Commercial lots are comparable ([Section P.2.3.3](#)),

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BLA761070, Benralizumab, Prefilled Syringe

AstraZeneca

thereby supporting the use of the clinical lots as the primary lots to support stability of the commercial lots. Stability studies for the primary and commitment lots include the long-term storage condition of 2-8°C, an accelerated condition of 23-27°C /55-65% relative humidity (RH) and a stressed condition of 38-42°C /70-80% RH. All the stability results at the long-term storage condition met the Process 3 Commercial acceptance criteria.

The proposed shelf life for Drug Product is based on available long-term, real-time stability data per ICH Q5C. The proposed Drug Product shelf life at the long-term storage condition of 2-8°C is ^{(b) (4)} months.

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Table P.8.1.2.2-3 Drug Product Stability Tests and Testing Intervals for Primary Lots

Tests	Testing Intervals (months)									
	0	1	2	3	6	9	12	18	24	36
2-8°C										
Total protein	●	●	○	●	●	●	●	●	●	●
pH	●	●	○	●	●	●	●	●	●	●
Appearance	●	●	○	●	●	●	●	●	●	●
Reducing gel electrophoresis	●	●	○	●	●	●	●	●	●	●
Non-reducing gel electrophoresis	●	●	○	●	●	●	●	●	●	●
HPSEC	●	●	○	●	●	●	●	●	●	●
cIEF	●	●	○	●	●	●	●	●	●	●
Reporter gene bioassay	●	●	○	●	●	●	●	●	●	●
Sub-visible particles	●	○	○	● ^a	●	○	●	○	●	●
Deliverable volume	●	● ^a	○	● ^a	●	○	●	○	●	●
Container Closure Integrity	●	○	○	● ^a	●	○	●	○	●	●
Sterility	●	○	○	○	○	○	●	○	○	●
Break-loose / Glide Force	●	●	○	●	●	○	●	○	●	●
Rigid Needle Shield Removal Force	●	●	○	●	●	○	●	○	●	●
23-27°C/55-65% RH										
Total protein	●	●	● ^a	●	●	○	○	○	○	○
pH	●	●	● ^a	●	●	○	○	○	○	○
Appearance	●	●	● ^a	●	●	○	○	○	○	○
Reducing gel electrophoresis	●	●	● ^a	●	●	○	○	○	○	○
Non-reducing gel electrophoresis	●	●	● ^a	●	●	○	○	○	○	○
HPSEC	●	●	● ^a	●	●	○	○	○	○	○
cIEF	●	●	● ^a	●	●	○	○	○	○	○
Reporter gene bioassay	●	●	● ^a	●	●	○	○	○	○	○
Sub-visible particles	●	● ^b	○	○	● ^b	○	○	○	○	○
Deliverable volume	●	●	○	●	●	○	○	○	○	○
Container Closure Integrity	●	●	○	● ^a	●	○	○	○	○	○
Sterility	●	○	○	○	○	○	○	○	○	○
Break-loose / Glide Force	●	●	○	●	●	○	○	○	○	○
Rigid Needle Shield Removal Force	●	●	○	●	●	○	○	○	○	○
38-42°C/70-80% RH										
Total protein	●	●	●	●	○	○	○	○	○	○
pH	●	●	●	●	○	○	○	○	○	○
Appearance	●	●	●	●	○	○	○	○	○	○
Reducing gel electrophoresis	●	●	●	●	○	○	○	○	○	○
Non-reducing gel electrophoresis	●	●	●	●	○	○	○	○	○	○
HPSEC	●	●	●	●	○	○	○	○	○	○

Table P.8.1.2.2-3 Drug Product Stability Tests and Testing Intervals for Primary Lots

Tests	Testing Intervals (months)									
	0	1	2	3	6	9	12	18	24	36
cIEF	•	•	•	•	○	○	○	○	○	○
Reporter gene bioassay	•	•	•	•	○	○	○	○	○	○
Sub-visible particles	•	○	○	• ^b	○	○	○	○	○	○
Deliverable volume	•	• ^a		•	○	○	○	○	○	○
Break-loose / Glide Force	•	○	○	•	○	○	○	○	○	○
Rigid Needle Shield Removal Force	•	○	○	•	○	○	○	○	○	○

cIEF = capillary isoelectric focusing; HPSEC = high performance size exclusion chromatography; RH = relative humidity; • = Scheduled; ○ = Not Performed

^a Only performed for DSP-563304 and DSP-563305.

^b Performed only on SP-01125 and SP-01175.

Reviewer’s Comments: The Sponsor has provided adequate release specifications.

10.RECOMMENDATION

The BLA application, applicant IR responses and the device constituent parts related DMFs have provided adequate container closure system information and acceptable functional performance test reports. The consulting reviewer has determined that the device constituent parts of the combination product have been designed appropriately for the product’s intended use and essential performance requirements.

11. Interactive review

One interactive review deficiency was sent to the Sponsor on August 2, 2017.

1. In your application you have provided functional performance tests for the accessorized prefilled syringe (APFS). You also state that you have followed the FDA guidance document, Medical Devices with Sharps Injury Prevention Features and ISO Standard 23908. I was unable to locate the performance test reports for the APFS sharps injury prevention feature. In the FDA guidance document it recommends using 500 samples with zero failures for acceptable results. Please provide the completed test reports for the sharps injury prevention for our review. This information is necessary to ensure the APFS in BLA 761070 will protect the health care provider from accidental needle stick injuries.

Sponsor’s Response 8-18-2017, sequence 0026:

The ^{(b) (4)} Needle Guard is a 510(k) FDA cleared medical device ^{(b) (4)} ^{(b) (4)} This device has been cleared by the FDA to provide protection from accidental needle stick injury, and it has been commercially marketed worldwide ^{(b) (4)} with numerous products. This device was selected,

in part, because it is a 510(k) cleared medical device that was successfully tested by (b) (4) in accordance with worldwide regulatory guidance and because of its extensive commercial market usage. Please refer to FDA cleared 510(k)s, (b) (4) for the testing conducted to support this intended use, including the testing conducted to fulfill FDA guidance and ISO 23908. Refer to the (b) (4) summary of FDA guidance, (b) (4) 510(k) and (b) (4) quality statement regarding ISO 23908:2011. In addition, the (b) (4) Needle Guard was tested as part of benralizumab Design Verification (DV) during combination product development. Override Force and Needle Access were tested to assess needle stick prevention. The Override Force testing consisted of measurement of vertical load applied on the locked safety feature of the (b) (4) (b) (4) Needle guard. The Needle Access testing was conducted with 6mm ball radius which was positioned against the safety feature of the device per ISO 23908, (b) (4). Sample sizes were selected based on a risk based approach. A specific risk level corresponds to a desired confidence and reliability and determines the sample sizes used based on our risk management plan. In total, 219 samples of the benralizumab combination product were tested in various conditions with zero failures (Table 1.11.1-1).

Table 1.11.1-1 Needle Sharps Protection- Testing Summary

Storage Conditions 5°C	At Use Conditions 23°C	Post transport simulation, Shock & Vibration	Post transport simulation, Shock& Vibration, and drop test(n)	Total tested	Number of Failures
n=29 (Override Force)	n=29 (Override Force)	n=29 (Override Force) 20 ^b (Needle Access& Override Force)	n=28, n=29, n=15, n=5 ^a (Override Force tested at multiple drop orientations) n=15 ^b (Override Force) n=20 ^b (Needle Access& Override Force)	219	0

^a Device drop (without carton)

^b Carton drop (Device within its packaging)

Based on extensive use of the device in previously FDA approved drug products, independent clearance of the device as a sharps protection system, and the data generated during benralizumab DV testing, the effectiveness of the (b) (4) Needle guard for needle stick prevention with benralizumab APFS has been adequately established.

(b) (4)

Summary of FDA Guidance/
(b) (4) **needle guards 510(K)s**

Device	Submission Type	510(K)	510(K) Clearance Date	Stimulated Clinical Use Testing Filed with FDA (510(k) Reference Section)
(b) (4) needle guard	Traditional 510k	(b) (4)	(b) (4)	As per FDA Draft Supplementary Guidance on the <i>Content of Premarket Notification {510(k)} Submissions for Medical Devices with Sharps Injury Prevention Features</i> , March 1995, each of the specified acceptance criteria in the controlled simulated clinical use test were either met or exceeded. Stimulated clinical trials were based on predicative devices (b) (4)
(b) (4) needle guard {Expansion of Indications for Use}	Traditional 510k			No additional sharps injury prevention testing required for this premarket notification.
(b) (4) needle guard {New Materials for Plunger Rod}	Special 510k			As per FDA Guidance <i>Medical Devices with Sharps Injury Prevention Features</i> , "If your sharps injury prevention feature is currently legally marketed as a part of another device, you may identify that device in lieu of performing simulated clinical use testing." SSI relies on the clinical use studies completed for the legally marketed devices as well as additional simulated use study for the addition of the various plungers. As per FDA guidance and ISO 23908, 168 devices were tested with zero failures. (b) (4)
(b) (4) needle guard {New Design}	Traditional 510k			As per FDA Guidance <i>Medical Devices with Sharps Injury Prevention Features</i> , 500 devices were tested with zero failures for a "97.5% confident that the true failure rate was no higher than 0.7% and 99.5% confidence that it is no higher than 1.1%". (b) (4)

CDRH Response/Discussion: T resolved.

ded an adequate response to the IR. Deficiency

**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: July 31, 2017

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)

Sharon Williams, MSN, BSN, RN
Acting Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Drug Name (established name): TRADENAME (benralizumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761070

Applicant: AstraZeneca Pharmaceuticals LP, Authorized U.S. Agent for AstraZeneca AB

1 INTRODUCTION

On November 16, 2016, AstraZeneca Pharmaceuticals LP, Authorized U.S. Agent for AstraZeneca AB, submitted for the Agency's review an Original Biologics License Application (BLA) 761070 for TRADENAME (benralizumab) injection. The proposed indication for TRADENAME (benralizumab) injection is as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype.

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 January 6, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (benralizumab) injection.

2 MATERIAL REVIEWED

- Draft TRADENAME (benralizumab) injection PPI received on November 16, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 11, 2017.
- Draft TRADENAME (benralizumab) injection Prescribing Information (PI) received on November 16, 2016, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 11, 2017.
- Approved NUCALA (mepolizumab) for injection comparator labeling dated February 16, 2017.
- Approved CINQAIR (reslizumab) injection comparator labeling dated March 23, 2016.

3 REVIEW METHODS

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.

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.

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

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

/s/

KAREN M DOWDY
07/31/2017

KYLE SNYDER
08/01/2017

SHARON W WILLIAMS
08/01/2017

LASHAWN M GRIFFITHS
08/01/2017

LABEL AND LABELING AND HUMAN FACTORS 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: July 14, 2017

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

Application Type and Number: BLA 761070

Product Name and Strength: Benralizumab
Injection
30 mg/mL

Product Type: Drug-Device Combination Product

Rx or OTC: Rx

Applicant/Sponsor Name: AstraZeneca

Submission Date: November 16, 2016 & February 1, 2017

OSE RCM #: 2016-2791 & 2016-2943

DMEPA Primary Reviewer: Matthew Barlow RN, BSN

DMEPA Team Leader: Sarah K. Vee, PharmD

DMEPA Associate Director for Human Factors: QuynhNhu Nguyen, MS

OMEPRM Acting Deputy Director: Lubna Merchant, MS, PharmD

1 REASON FOR REVIEW

This review is in response to a request by DGIEP for DMEPA to evaluate the container labels, carton labeling, prescribing information (PI), and human factors (HF) information for benralizumab injection, submitted under BLA 761070. The sponsor submitted the proposed container labels, carton labeling, prescribing information, and HF information on November 16, 2016.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Human Factors/Use Related Risk Analysis

Astrazeneca submitted BLA 761070 as a 351(a) on November 16, 2016 for the intended use as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype. The proposed commercial product is 30 mg/mL accessorized pre-filled syringe (APFS). The APFS consists of a (b) (4)

(b) (4)
the
intended user population for this product is HCPs only.

The applicant included a summary of the formative studies, (b) (4)
(b) (4) and final usability study that had been conducted with their November 16, 2016 BLA submission. However, this submission did not include all the information required. Thus, in the 74-day letter sent out on January 27, 2017 DMEPA included an information request (IR) for

an updated use related-risk analysis (URRA) for the proposed product, a detailed HF validation study report, intend-to-market samples of the product, and a summary of any changes made to the user interface (e.g., product design or label and labeling changes) after completion of the human factors validation study, including a description of how the changes were validated. The sponsor responded to our IR on February 1, 2017 with an updated URRA, five intend-to-market samples of the product, a summary of any changes made to the user interface after the completion of the HF validation study. The sponsor felt the use risks for HCP-only administration in the clinical setting were acceptably low and did not require HF validation testing. We find that:

- 1) the proposed prefilled syringe is identical to a standard prefilled syringe
- 2) the updated use related-risk analysis did not identify any new or unique risk for use with this product

Label and Labeling

The sponsor submitted the proposed commercial and professional sample carton labels, lidding labels, syringe labels, and prescribing information on November 16, 2016. We performed a risk assessment of the submitted labels and labeling for areas of vulnerability that may lead to medication errors. We note the proposed labels and labeling can be improved to increase the prominence and clarity of important information. We note the established name lacks prominence when compared with the proprietary name, which is inconsistent with regulation. Also, we note the storage information on the principal display panel (PDP) can be revised to emphasize this important information. Additionally, we note the professional sample statements could be revised to better emphasize this information. We provide letter ready recommendations in section 4.1 below.

Nonproprietary Name

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

4 CONCLUSION & RECOMMENDATIONS

We concur that an HF validation study is not required. We conclude that the proposed labels and labeling can be improved to increase the prominence, readability, and clarity of important information and promote the safe use of the product and mitigate confusion. Please see recommendation below.

4.1 RECOMMENDATIONS FOR ASTRAZENECA

General Comments

1. FDA issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying a decision on the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your BLA be licensed, and intend to work with you post-approval to implement a proper name consistent with the principles outlined in the guidance. We would work with you to minimize the impact this would have to your manufacture and distribution of this product.
2. Once a proprietary name has been found conditionally acceptable, replace the placeholder "Tradenam" throughout the PI and all the commercial and professional sample carton labels, lidding labels, and syringe labels with the conditionally acceptable proprietary name and resubmit.

A. All Commercial and Professional Sample Labels

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name by using bold typeface in accordance with 21 CFR 201.10(g)(2).

B. Commercial and Professional Sample Carton and Lidding Labels

1. Revise and bold the statement [REDACTED] (b) (4) to read as follows [REDACTED] (b) (4). We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

C. Professional Sample Carton Label

1. Revise the statement "PROFESSIONAL SAMPLE – NOT FOR SALE" with bold typography to emphasize this important information.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Benralizumab that Astrazeneca submitted on November 16, 2016.

Table 2. Relevant Product Information for Benralizumab	
Initial Approval Date	N/A
Active Ingredient	benralizumab
Indication	indicated as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype
Route of Administration	subcutaneous
Dosage Form	injection
Strength	30 mg/mL
Dose and Frequency	recommended dose is 30 mg administered once every 4 weeks for the first 3 doses, and then once every 8 weeks thereafter by subcutaneous injection
How Supplied	supplied as a sterile, preservative-free, clear to opalescent, colorless (b) (4) solution for subcutaneous injection in cartons of 1 single-use prefilled syringe. carton contains one (b) (4) single-dose prefilled syringe: NDC 0310-1730-30
Storage	store refrigerated at 2°C to 8°C (36°F to 46°F). Store the prefilled syringe in the original package in order to protect from light. Do not freeze. Do not shake.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 25, 2017, we searched the L:drive and AIMS using the terms, benralizumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 1 previous review^a, which is not applicable for this review.

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

^a Owens, L. Human Factors Protocol Review for Benralizumab IND 100237. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 JUN 03. RCM No.: 2015-929.

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/s/

MATTHEW J BARLOW
07/17/2017

SARAH K VEE
07/17/2017

MISHALE P MISTRY on behalf of QUYNHNHU T NGUYEN
07/17/2017

LUBNA A MERCHANT
07/17/2017

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

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

Memorandum

Date: July 14, 2017

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

From: Kyle Snyder, Pharm.D.
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 761070
OPDP comments on draft PI, PPI, and carton/container labels for benralizumab injection, for subcutaneous use

Reference is made to DPARP's consult request dated January 6, 2017, requesting review of the proposed Package Insert (PI), Patient Package Insert (PPI), and carton/container labels for benralizumab injection, for subcutaneous use.

OPDP has reviewed the proposed draft PI entitled "761070 benralizumab clean-draft-label.doc" that was received via email from Colette Jackson on July 11, 2017. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has reviewed the following proposed carton/container labels received on November 16, 2016:

- Draft Carton 30 mg Clean.pdf
- Draft Carton 30 mg Sample Clean.pdf
- Draft Lidding 30 mg Clean.pdf
- Draft Lidding 30 mg Sample Clean.pdf
- Draft Syringe 30 mg Clean.pdf
- Draft Syringe 30 mg Sample Clean.pdf

OPDP notes that the net quantity is presented as “1 single-dose prefilled syringe” in conjunction with the strength, 30 mg/mL; and the contents list [REDACTED] (b) (4). However, the labels do not indicate the volume of drug contained in each prefilled syringe. OPDP recommends revising the carton labels to include this material information and revising the lidding and syringe labels as space permits.

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

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions or concerns, please contact Kyle Snyder at 240-402-8792 or kyle.snyder@fda.hhs.gov.

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/s/

KYLE SNYDER
07/14/2017

CLINICAL INSPECTION SUMMARY

Date	June 1, 2017
From	Anthony Orenca M.D., F.A.C.P., GCPAB Medical Officer Cynthia Kleppinger, M.D., Acting Team Leader, for Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H. GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Sofia Chaudhry, M.D., Medical Officer Lydia Gilbert McClain, M.D., Supervisory Medical Officer Colette Jackson, Senior Regulatory Project Manager Division of Pulmonary, Allergy and Rheumatology Products
BLA	761070
Applicant	AstraZeneca
Drug	benralizumab
NME	Yes
Therapeutic Classification	505b1 (Human monoclonal antibody to IL-5R α receptor)
Proposed Indication	Add-on maintenance treatment for patients with severe asthma and with an eosinophilic phenotype
Consultation Request Date	February 2, 2017
Summary Goal Date	June 15, 2017
Action Goal Date	November 16, 2017
PDUFA Date	November 16, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Kureishy and Maddock) and the sponsor AstraZeneca were selected by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for inspection of Study D3250C00017 and Study D3250C00018, in support of BLA 761070. The study data derived from the two clinical sites and the sponsor are considered reliable in support of the requested indication.

The final CDER regulatory classification for Dr. Maddock is No Action Indicated (NAI). The preliminary regulatory classification of the inspections of the sponsor and Dr. Kureishy is NAI.

2. BACKGROUND

Current FDA-approved neutralizing anti-IL-5 antibodies (mepolizumab and reslizumab) used in the treatment of patients with (b) (4) eosinophilic asthma may result in an improvement in asthma control. In contrast to the mechanism of action of mepolizumab and reslizumab, benralizumab (MEDI-563) is a humanized, afucosylated, monoclonal antibody that binds specifically to the human IL-5 receptor alpha subunit (IL-5R α) on the target cell. The afucosylation process confers antibody-dependent cellular cytotoxicity (ADCC), which results in eosinophil depletion by apoptosis. This subsequent depletion is proposed by the sponsor to be associated with improvement in severe (b) (4) asthma control, as part of maintenance therapy.

Two randomized clinical trials D3250C00017 and D3250C00018 submitted in support of the applicant's BLA for the treatment of patients with chronic uncontrolled asthma, ages 12 years and above, were selected for inspection.

CDER DPARP requested a single domestic clinical site in Study D3250C00017, a single domestic site in Study D3250C00017, and the sponsor for inspection. These sites principally enrolled large numbers of study subjects, had differential efficacy findings across the clinical study sites, and other study risks as assessed by CDER DPARP.

Study D3250C00017

Study D3250C00017 was a randomized, double-blind, parallel group, placebo-controlled, multicenter Phase 3 study to assess the efficacy and safety of benralizumab (MEDI-563), as part of the maintenance therapy for uncontrolled (severe) chronic asthma in patients aged 12 to 75 years. Adult patients and adolescent patients were randomized to either placebo or one of two dosing regimens of benralizumab, 30 mg every 4 weeks or 30 mg every 8 weeks. This fixed 30 mg dose of benralizumab was administered subcutaneous for 48 weeks in patients with uncontrolled asthma despite treatment with inhaled corticosteroid and long acting beta 2 agonist (LABA) therapy, or other therapy.

To evaluate the effect of the two dosing regimens of benralizumab on asthma exacerbations, the primary efficacy endpoint was annual asthma exacerbation rate. Asthma exacerbation was defined as a worsening of asthma requiring: (1) use of systemic corticosteroids (or a temporary increase in a stable oral corticosteroid background dose) for at least three days; a single depo-injectable dose of corticosteroids was considered equivalent to a three-day course of systemic corticosteroids, (2) emergency room or urgent care visit (defined as evaluation and treatment for less than 24 hours in an emergency department or urgent care center) due to asthma that required systemic corticosteroids (as per above), or (3) an inpatient hospitalization due to asthma (defined as an admission to an inpatient facility and/or evaluation and treatment in a healthcare facility for at least 24 hours).

The study randomized 1205 patients stratified by age group (adult or adolescent), country/region (within EU/outside EU for adolescents) and peripheral blood eosinophil count (below or at least

300/ μ L). Patients were enrolled at 374 centers in 17 countries; 286 of these centers in all 17 countries randomized at least a single patient. The first patient enrolled September 19, 2013 and the last patient visited was April 5, 2016.

Study D3250C00018

Study D3250C00018 was a randomized, double-blind, parallel group, placebo-controlled Phase 3 study to assess the efficacy and safety of benralizumab (MEDI-563), as part of the maintenance therapy for uncontrolled (severe) chronic asthma in patients aged 12 to 75 years. Adult and adolescent patients were randomized to receive double-blind treatment (double-dummy technique) of either placebo or one of two dosing regimens of benralizumab 30 mg, those being every 4 weeks throughout the treatment period *versus* every 4 weeks for the first 3 doses followed by every 8 weeks thereafter. This fixed 30 mg dose of benralizumab was administered subcutaneous for 56 weeks in patients with severe chronic asthma on LABA and inhaled corticosteroid therapy, or other therapy

The primary efficacy endpoint was the annual asthma exacerbation rate (annualized exacerbation rate) and the primary analysis was to compare the unadjudicated annual asthma exacerbation rate (based on data reported by the investigator in the electronic case report form) of each benralizumab dose regimen with placebo in high-dose inhaled patients with baseline blood eosinophil counts at least 300/ μ L.

Of the 1306 patients randomized, all subjects received treatment with study drug: 425, 441, and 440 patients received benralizumab 30 mg every 4 weeks, every 8 weeks, and placebo, respectively. Patients were enrolled at 303 centers in 11 countries; 242 of these centers in all 11 countries randomized at least a single patient. The first patient enrolled August 21, 2013 and the last study patient's visit was March 11, 2016.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site ## Subjects	Inspection Date	Classification
Shahrukh Kureishy, M.D. Metroplex Pulmonary & Sleep Medicine Center, PA 4833 Medical Center Dr Suite 6B McKinney, TX 75069	D3250C00017 Site # 7802 Subjects = 6	April 25 to 28, 2017	Preliminary NAI
Stephen Maddock, MD, Ph.D. Analab Clinical Research Inc. 15335 W 95th Street Lenexa, KS 66219	D3250C00018 Site# 7805 Subjects = 6	March 8 to 10, 2017	NAI
AstraZeneca 4222 Emperor Blvd, Suite 560 Durham, NC 27703	Sponsor for studies: D3250C00017 D3250C00018	May 17 to 18, 2017	Preliminary NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Shahrukh Kureishy, M.D./Study D3250C00017/Site # 7802

The inspection was conducted from April 25 to 28, 2017. A total of 37 subjects were screened, and six subjects were enrolled and randomized. One subject withdrew further participation from the study. Five subjects completed the study. An audit of the six randomized subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.

2. Stephen Maddock, M.D., Ph.D./Study D3250C00018 /Site # 7805

The inspection was conducted from March 8 to 10, 2017. A total of 26 subjects were screened, and six subjects were enrolled and randomized. Two subjects were study discontinuations: one patient became pregnant, and another patient developed a rash. Four study subjects completed the study. An audit of the six randomized subjects' records enrolled at this site was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. No Form FDA 483 was issued.

Sponsor

3. AstraZeneca

This inspection was conducted from May 17 to 18, 2017.

The sponsor inspection included review of the following: regulatory site set up, financial disclosures, site management and monitoring, electronic Trial Master File (eTMF), functional services, and the Clinical Trial Management System (CTMS).

Monitoring plans and visits including study site closeout were reviewed; monitoring reports indicated that the sites received adequate periodic monitoring. IRB approvals, site study protocol deviations, serious adverse events and related monitoring reports were assessed, and oversight by the sponsor appeared to be adequate. There were no under-reporting of serious adverse events.

A Form FDA 483 was not issued at the end of the inspection. The sponsor maintained adequate oversight of the clinical trials.

{See appended electronic signature page}

Anthony Orenca, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Cynthia Kleppinger, M.D., for
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/s/

ANTHONY J ORENCIA
06/02/2017

CYNTHIA F KLEPPINGER
06/02/2017

KASSA AYALEW
06/02/2017

**Selected Requirements of Prescribing Information
REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION**

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

Application: BLA 761070

Application Type: New BLA

Drug Name(s)/Dosage Form(s): [Benralizumab](#)

Applicant: AstraZeneca

Receipt Date: November 16, 2016

Goal Date: November 16, 2017

1. Regulatory History and Applicant's Main Proposals

AstraZeneca Pharmaceuticals submitted a new biologic application for Benralizumab, Benralizumab is a humanised, afucosylated, monoclonal antibody. Benralizumab is 30 mg in 1.0 mL solution for injection in a prefilled syringe. The proposed indication is as an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype. In this new application, AstraZeneca 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 of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

Selected Requirements of Prescribing Information

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

- 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), **and**
 - TOC from the Full Prescribing Information (FPI).

Comment:

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

Comment:

- 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 for HL format.

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

Heading	Required/Optional
• Highlights Heading	Required

Selected Requirements of Prescribing Information

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

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

- N/A** 13. The BW must have a title in UPPER CASE, following the word “**WARNING**” and other words to identify the subject of the warning. Even if there is more than one warning, the term

Selected Requirements of Prescribing Information

“WARNING” and not “WARNINGS” should be used. For example: “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”. If there is more than one warning in the BW title, the word “and” in lower case can separate the warnings. The BW title should be centered.

Comment:

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

Comment:

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

Comment:

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Contraindications in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

- YES** 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**”

Comment:

Patient Counseling Information Statement in Highlights

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

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

- See 17 for **PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

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

Comment:

Revision Date in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

- YES** 24. The TOC should be in a two-column format.
Comment:
- YES** 25. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS.**” This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 26. The same title 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** 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].
Comment:
- YES** 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading “**FULL PRESCRIBING INFORMATION: CONTENTS***” must be followed by an asterisk and the following statement must appear at the end of the TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "Labor and Delivery")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "Nursing Mothers")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].”

Comment:

Selected Requirements of Prescribing Information

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

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

- N/A** 39. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

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

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
- Advise the patient to read the FDA-approved patient labeling (Patient Information).
 - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
 - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

- YES** 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: TITLE OF WARNING

See full prescribing information for complete boxed warning.

- Text (4)
- Text (5.x)

RECENT MAJOR CHANGES

Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

INDICATIONS AND USAGE

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

Limitations of Use: Text (1)

DOSAGE AND ADMINISTRATION

- Text (2.x)
- Text (2.x)

DOSAGE FORMS AND STRENGTHS

Dosage form(s): strength(s) (3)

CONTRAINDICATIONS

- Text (4)
- Text (4)

WARNINGS AND PRECAUTIONS

- Text (5.x)
- Text (5.x)

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- Text (7.x)
- Text (7.x)

USE IN SPECIFIC POPULATIONS

- Text (8.x)
- Text (8.x)

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

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: TITLE OF WARNING

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Subsection Title

2.2 Subsection Title

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Subsection Title

5.2 Subsection Title

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Immunogenicity

6.2 or 6.3 Postmarketing Experience

7 DRUG INTERACTIONS

7.1 Subsection Title

7.2 Subsection Title

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation (if not required to be in PLLR format use Labor and Delivery)

8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format use Nursing Mothers)

8.4 Pediatric Use

8.5 Geriatric Use

8.6 Subpopulation X

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 Subsection Title

14.2 Subsection Title

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
01/26/2017

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# 761070	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: benralizumab Dosage Form: Injection Strengths: 30 mg/mL Route(s) of Administration: Subcutaneous		
Applicant: AstraZeneca AB Agent for Applicant (if applicable): AstraZeneca Pharmaceuticals LP		
Date of Application: November 16, 2016 Date of Receipt: November 16, 2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA Goal Date: November 16, 2017	Action Goal Date (if different):	
Filing Date: January 15, 2017	Date of Filing Meeting: January 11, 2017	
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 <input type="checkbox"/> Type 9-New Indication or Claim (will <u>not</u> be marketed as a separate NDA after approval) <input type="checkbox"/> Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication: As an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype.		
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)NDA/NDA Supplement: 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 <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			
The application will be a priority review if: <ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 					
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>			
Part 3 Combination Product? <input type="checkbox"/> If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)			
<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):					
List referenced IND Number(s): 100237					
Goal Dates/Product Names/Classification Properties		YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.		<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in electronic archive? If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.		<input checked="" type="checkbox"/>	<input type="checkbox"/>		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Emailed document room 1/6/17.
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC 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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.</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. Contact the User Fee Staff. If appropriate, send UN letter.</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: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</i>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form, cover letter, and annotated labeling</i>). If yes , answer the bulleted questions below:	<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	<input type="checkbox"/>	<input type="checkbox"/>		

<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p>	<input type="checkbox"/>	<input type="checkbox"/>																		
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%;">Application No.</th> <th style="width: 30%;">Drug Name</th> <th style="width: 25%;">Exclusivity Code</th> <th style="width: 20%;">Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<ul style="list-style-type: none"> If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement [see 21 CFR 314.50(i)(1)(i)(C) and 314.54]? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If no, include template language in the 74-day letter.</p> <p>Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]</p> <p><i>Note: Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>																		

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 checked="" type="checkbox"/>		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(14)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
NDA/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
NDA 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"/>	

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<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)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>Index: Does the submission contain an accurate comprehensive index?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA</i>s/<i>NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLA</i>s/<i>BLA efficacy supplements</i>) including:</p> <p><input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain.</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>BLAs only: Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Forms and Certifications				
<p><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.</i> 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.</p>				
Application Form	YES	NO	NA	Comment
<p>Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?</p> <p><i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>Are all establishments and their registration numbers listed on the form/attached to the form?</p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

¹ <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf>

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)? <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
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
<p>For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p>For non-NMEs: <i>Date of consult sent to Controlled Substance Staff:</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<p>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<p>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><u>BPCA:</u></p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required³</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

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

3

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

Version: 12/05/2016

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Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	PNR not submitted with BLA, but recently under IND. Company contacted
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (Prescribing Information)(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 labeling <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent labeling <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in Physician Labeling Rule (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 type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	<input checked="" type="checkbox"/> <input checked="" type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input 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 PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm>

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <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)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	CDRH Consults sent by OBP on January 5, and 6, 2017.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): February 13, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): September 20, 2016	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>			

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 11, 2017

BACKGROUND: AstraZeneca AB is submitting an original BLA for benralizumab for the following indication: As an add-on maintenance treatment for patients with severe asthma aged 18 years and older, with an eosinophilic phenotype.

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)	Lydia Gilbert-McClain		N
Division Director/Deputy	Badrul A. Chowdhury		Y
Office Director/Deputy	Curtis Rosebraugh Mary Thanh Hai		Y- Mary
Clinical	Reviewer:	Sofia Chaudhry	Y
	TL:	Lydia Gilbert-McClain	N
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:	Sury Sista	Y
	TL:	Anshu Marathe	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Jade Wang	Y
	TL	Gregory Levin	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Timothy Robison	Y
	TL:	Carol Galvis	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Sarah Kennett	Y
	RBPM:	Kelly Ballard	Y
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:	Jenni Swisher	Y
• Process	Reviewer:		
• Microbiology	Reviewer:	Maria Barragon Maria Fisher	Y
• Facility	Reviewer:	Li Zhong	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Matt Barlow	N
	TL:	Mishale Mistry	N
OSE/DRISK (REMS)	Reviewer:	Charlotte Jones	Y
	TL:	Donella Fitzgerald	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> DPV <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:	Dipti Kalra	Y
	TL:	Eileen Wu	N
<ul style="list-style-type: none"> DEPI <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:	Veronica Sansing-Foster	Y
	TL:	Margie Goulding	N
Other attendees	OSE RPM Michael Sinks		Y
	Banu Karimi Shah		Y
	Erika Torjusen		Y
	*For additional lines, right click here and select "insert rows below"		

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., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</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:</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 type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: This drug/biologic is not the first in its class. Reslizumab and Mepolizumab previously approved
<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

CLINICAL PHARMACOLOGY 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
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS Comments:	<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
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) 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
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> <ul style="list-style-type: none"> Is the product an NME? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Facility Inspection</u> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Curtis Rosebraugh, M.D.

Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): April 27, 2017

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review</p>

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 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: April 2016

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
01/26/2017