

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125526Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

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

NDA/BLA # BLA# 125526
Product Name: Mepolizumab

PMR/PMC Description: A 12 week, randomized, open-label, pharmacokinetic and pharmacodynamics study of mepolizumab in pediatric patients with asthma 6 to 11 years of age (Part A of Study 200363)

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/30/2015</u>
	Study Completion:	<u>9/30/2017</u>
	Final Report Submission:	<u>9/30/2019</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

Mepolizumab is read for approval in patients 12 years and older. Pediatric PREA studies in children 6-11 years of age were deferred at the time of approval.

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

The goal of the study is to evaluate the pharmacokinetics and pharmacodynamics of mepolizumab in patients 6 to 11 years of age. (b) (4)

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?

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

- Analysis using pharmacovigilance system?

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

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

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

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

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

The study is a pharmacokinetic/pharmacodynamics of mepolizumab in children 6-11 years of age.

(b) (4)

Required

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

Continuation of Question 4

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

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

Agreed upon:

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

-
- Other
-

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

The goal of the study is to evaluate the long term safety in patients 6 to 11 years of age.

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

If not a PMR, skip to 4.

– **Which regulation?**

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

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

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

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

Analysis of spontaneous postmarketing adverse events?

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

Analysis using pharmacovigilance system?

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

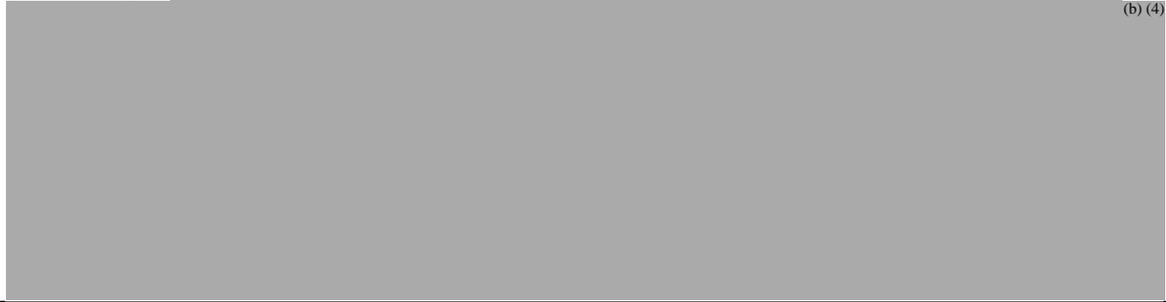
Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

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

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

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

The study is a long term extension to collect safety and pharmacodynamics data in children 6-11 years of age. (b) (4)



Required

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

Continuation of Question 4

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

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

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?

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

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

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

NDA/BLA # 125526 Nucala (mepolizumab)
Product Name:

PMC #1 Description: To qualify the bioburden test at the (b) (4) in the drug product manufacturing process using a sample volume of 100 mL and to implement a (b) (4) bioburden limit of (b) (4)/100 mL. Submit the qualification and implementation of this bioburden test as a CBE-0.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>06/30/2016</u>
	Other:	<u>MM/DD/YYYY</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

Currently, the (b) (4) bioburden limit is (b) (4). Current industry practice is to set the (b) (4)/100 mL. The sponsor has agreed qualify the bioburden test at the (b) (4) using a sample volume of 100 mL and to implement a bioburden limit of (b) (4)/100 mL. Adequate microbial controls are in place; therefore this is not an approvability issue.

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

The (b) (4) bioburden limit is (b) (4). Improved product quality can be ensured by tightening the (b) (4) limits for bioburden at this step in the manufacturing process.

3. [OMIT – for PMRs only]

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

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

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

Describe the agreed-upon study:

The sponsor will qualify the bioburden test at the (b) (4) in the drug product manufacturing process using a sample volume of 100 mL and implement a (b) (4) bioburden limit of (b) (4)/100 mL. The qualification and implementation of this bioburden test will be submitted as a CBE-0 supplement by June 30, 2016.

5. To be completed by ONDQA/OBP Manager:

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs only)

This 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
11/03/2015



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

FINAL LABEL AND LABELING REVIEW

Date:	October 22 2015
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad -S <small>Digitally signed by Jibril Abdus-samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=2342.19200300.100.1.1=1300439425, cn=Jibril Abdus-samad -S Date: 2015.10.22 11:42:26 -04'00'</small>
Through:	Marjorie Shapiro, PhD, Quality Reviewer, Lab Chief Division of Biotechnology Review and Research I Marjorie A. Shapiro -S <small>Digitally signed by Marjorie A. Shapiro -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=2342.19200300.100.1.1=1300081252, cn=Marjorie A. Shapiro -S Date: 2015.10.23 12:09:36 -04'00'</small>
Application:	BLA 125526/0
Product:	Nucala™ (mepolizumab)
Applicant:	GlaxoSmithKline LLC
Submission Dates:	November 4 2014; August 13; September 15; October 16 2015

Executive Summary:

The container labels and carton labeling for Nucala™ (mepolizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [August 1 2015 to November 30 2015]. Labeling deficiencies were identified and resolved. The container labels and carton labeling submitted on September 15 2015 are acceptable.

Background and Summary Description:

The Applicant submitted BLA 125526 Nucala™ (mepolizumab) on November 4 2014. Table 1 lists the proposed product characteristics of Nucala™ (mepolizumab).

Table 1: Proposed Product Characteristics of Nucala™ (mepolizumab).

Proprietary Name:	Nucala™
Proper Name:	mepolizumab
Indication:	for add-on maintenance treatment of patients with asthma aged 12 years and older with (b) (4) (b) (4) (b) (4) (b) (4) and have applicable blood eosinophil counts.
Dose:	100 mg administered subcutaneously once every 4 weeks
Route of Administration:	subcutaneous
Dosage Form:	for injection
Strength and Container-Closure:	100 mg/vial
Storage and Handling:	Store below 25°C (77°F). Do not freeze. Store in the original package to protect from light.

Materials Reviewed:

Container Label submitted August 13 2015

Carton Label submitted August 13 2015

*the Applicant submitted trade and sample versions.

Start of Sponsor Material

Container Label (trade)

(b) (4)



Container Label (sample)

(b) (4)



End of Sponsor Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

Applicant's response in Times New Roman font
OBP decisions in Tahoma italics font.

I. Container

A. 21 CFR 610.60 Container Label

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

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

OBP Request: On the side panels, relocate the proper name, mepolizumab, to appear under the proprietary name, Nucala. Additionally, relocate the dosage form, for Injection, to appear under the proper name, mepolizumab. The proper name for CDER-regulated biological products should not include the finished dosage form. The finished dosage form, for Injection, can appear on the line below the proper name as displayed on the PDP and bottom panel. *Applicant revised as requested.*

(2) The name, address, and license number of manufacturer; does not conform. The Applicant is not labeled as the manufacturer.

OBP Request: The Applicant/Licensee on the 356h form is the licensed manufacturer per 21 CFR 600.3(t). The Applicant must appear as "Manufactured by". Additionally, the U.S. License Number must appear with the manufacturer information per 21 CFR 610.60(a)(2). Consider shortening the information on this vial due to the lack of space. Revise the manufacturer information to appear as:

Mfd by GlaxoSmithKline LLC, Philadelphia PA 19112
U.S. Lic. No. 1727
Applicant revised as requested.

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

(4) The expiration date; *conforms*.

(5) The recommended individual dose, for multiple dose containers; *not applicable*.

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

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

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

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

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

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

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

Applicant's September 15 2015 response: (b) (4)
label is (b) (4) applied on the vial leaving about (b) (4)
of uncovered area to permit inspection of the content across the
vial full length. *Applicant's response is acceptable.*

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; does not conform.

OBP Request: Relocate the NDC from the side panel to appear at the top of the PDP per 21 CFR 201.2 and 21 CFR 207.35. Specifically for the sample vial, relocate "Sample – Not for Sale" to the side panel. *Applicant revised as requested.*

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

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

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

F. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms.*

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

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

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

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

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

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

Start of Sponsor Material

Carton Labeling (trade)

(b) (4)



Carton Labeling (sample)

(b) (4)



End of Sponsor Material

Applicant's response in Times New Roman font
OBP decisions in Tahoma italics font.

II. Carton

A. 21 CFR 610.61 Package Label:

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

OBP Request: On the side panels, relocate the proper name, mepolizumab, to appear under the proprietary name, Nucala. Additionally, relocate the dosage form, for Injection, to appear under the proper name, mepolizumab. The proper name for CDER-regulated biological products should not include the finished dosage form. The finished dosage form, for Injection, can appear on the line below the proper name as displayed on the PDP and bottom panel¹. *Applicant revised as requested.*

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

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

Manufactured by:
GlaxoSmithKline LLC
5 Crescent Drive
Philadelphia PA 19112
U.S. License Number 1727
Applicant revised as requested.

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

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

d) The expiration date; *conforms*.

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

OBP Request: Add "No preservative" per 21 CFR 610.61(e).
Applicant revised as requested.

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

g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; does not conform.

OBP Request: On the rear panel, add the concentration of the reconstituted solution and deliverable volume with the reconstitution instructions. For example:

Reconstitute with 1.2 mL of Sterile Water for Injection, USP. Swirl gently for 10 seconds at 15-second intervals until dissolved. Do not shake. The reconstituted solution concentration is 100 mg/mL and delivers 1 mL.

Applicant revised as requested.

h) The recommended storage temperature; *conforms*.

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

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

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

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

- m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.
- o) The adjuvant, if present; *not applicable*.
- p) The source of the product when a factor in safe administration; *not applicable*.
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.
- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; does not conform.

OBP Request: Add "No U.S. standard of potency" to appear on the bottom label per 21 CFR 610.61(r).

Applicant revised as requested.

- s) The statement "Rx only" for prescription biologicals; *conforms*.
- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Not applicable*.

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

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

D. 21 CFR 610.64 Name and address of distributor:

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases: "Manufactured for _____". "Distributed by _____", "Manufactured by _____ for _____", "Manufactured for _____ by _____", "Distributor: _____", or "Marketed by _____". The qualifying phrases may be abbreviated. Does not conform. The licensed manufacturer does not appear on the labeling.

OBP Request: You may keep the name and address of the distributor on the labeling if the licensed manufacturer is listed above per 21 CFR 610.64. If you plan to include additional manufacturer information, provide the regulation(s) that you are attempting to fulfill.

Applicant revised as requested. The Applicant decided to include only the licensed manufacturer and distributor.

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

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

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

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

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

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

J. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

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

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

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

- N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.
- O. 21 CFR 201.55 Statement of dosage; *conforms*.
- P. 21 CFR 201.100 Prescription drugs for human use; *does not conform*.

OBP Request: Revise the statement "CONTENTS" to include all the ingredients per 21 CFR 201.100 and USP General Chapters <1091> Labeling of Inactive Ingredients.

Contents: Each vial delivers mepolizumab 100 mg, polysorbate 80 (0.67 mg), sodium phosphate, dibasic heptahydrate (7.14 mg), and sucrose (160 mg). After reconstitution with 1.2 mL of Sterile Water for Injection, USP, the reconstituted solution concentration is 100 mg/mL and delivers 1 mL.

Applicant revised as requested.

CDER Labeling Recommendations

This section describes additional recommendations provided to the Applicant that address CDER Labeling preferences.

A. General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials to comply with USP General Chapters: <7> Labeling, Labels and Labeling for Injectable Products, Ferrules and Cap Overseals. *Applicant confirmed*.
2. We note the inclusion of a bar code that links to an online instruction video for Nucala preparation. Provide rationale for including an instruction video for Nucala preparation considering reconstitution of lyophilized powder in a vial is a common task for healthcare practitioners that will prepare and administer this product. *See Discussion of Applicant's Proposals below.*

B. Vial Container Label (trade and sample)

1. Add the concentration of the solution after reconstitution. For example, "Reconstitute with 1.2 mL Sterile Water for Injection, USP resulting in a concentration of 100 mg/mL. *Applicant revised as requested.*

2. Revise the storage information to read: "Store below 25°C (77°F) in original carton to protect from light. Do not freeze." *Applicant revised as requested.*

Discussion of Applicant's Proposals

Bar Code for Preparation video

The Applicant proposes to include a barcode on the carton labeling that links to an online instruction video for Nucala preparation along with inclusion of a website (www.NucalaPrep.com) [REDACTED] (b) (4)

[REDACTED] We requested the Applicant provide rationale for including an instruction video for Nucala preparation considering reconstitution of lyophilized powder in a vial is a common task for HCPs that will prepare and administer Nucala.

Applicant's September 15 2015 response: The instructional video on reconstitution is meant to be a helpful aide to the health care professionals who must perform the reconstitution steps. In the setting of a specialty respiratory clinic, there can be a variety of experience among those asked to perform this task, even among those with appropriate training. The video is intended to reinforce appropriate technique for a protein product by following the instructions as on the USPI, including allowing sufficient time for dissolution and avoiding shaking.

We find the inclusion of the video may be helpful, however the preparation instructions on the proposed PI, container label, and carton labeling appear to adequately address the time for dissolution and avoidance of shaking. We recommend the Applicant include on the carton labeling (if space permits) and section 2 – DOSAGE AND ADMINISTRATION of the PI any preparation instructions that are relevant to the intended end-users in addition to the time for dissolution and avoidance of shaking.

The Applicant's placement of the bar code on the underside of the top panel of the carton labeling appears acceptable as it does not compete with or distract from the required or critical information on the carton labeling². [REDACTED] (b) (4)

[REDACTED] The Applicant's website can appear in the PI, unless the website is promotional in nature. [REDACTED] (b) (4)

[REDACTED], below the manufacturer information.

² Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2013 Apr. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

The website name, www.NucalaPrep.com, does not appear promotional. However, we defer to the Office of Prescription Drug Promotion's evaluation of the website name and content.

Subsequent to our labeling recommendations, the Applicant (b) (4)

Applicant's October 16, 2015 response: For instructions on reconstitution see (b) (4) or www.NUCALAPrep.com.

(b) (4), since preparation and administration of NUCALA is performed by a healthcare professional and not the patient.]

The Applicant did not update the preparation instructions with information that they deem relevant to the intended end-users in addition to the time for dissolution and avoidance of shaking. Thus, the required information for end-users to prepare NUCALA appears in section 2.2 of the PI and on the carton labeling. The inclusion of this video and website is supplemental and not required; therefore we still find the website should appear in the (b) (4)

Lastly, end-users can also access the website and 2D barcode that appears on the carton labeling.

Conclusions

The container labels and carton labeling for Nucala™ (mepolizumab) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100 and United States Pharmacopeia (USP), USP 38/NF 33 [August 1 2015 to November 30 2015]. Labeling deficiencies were identified and resolved. The container labels and carton labeling submitted on September 15 2015 are acceptable (see below).

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: September 24, 2015
Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number: BLA 125526
Product Name and Strength: Nucala (Mepolizumab) Powder for Injection, 100 mg per vial
Submission Date: August 13, 2015
Applicant/Sponsor Name: GlaxoSmithKline
OSE RCM #: 2014-2450
DMEPA Primary Reviewer: Lissa C. Owens, PharmD
DMEPA Team Leader: Kendra Worthy, PharmD

1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products requested that we review the revised carton and container labels (Appendix A) to determine if it is acceptable from a medication error perspective. The purpose of this submission is to amend the application with a revised logo. The Applicant replaced the (b) (4) logo.

2 CONCLUSIONS

The revised carton and container labels are acceptable from a medication error perspective.

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/s/

LISSA C OWENS
09/24/2015

KENDRA C WORTHY
09/25/2015

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

PATIENT LABELING REVIEW

Date: September 24, 2015

To: Badrul A. Chowdhury, MD, PhD
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products**

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

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

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

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

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

Drug Name (established name): NUCALA (mepolizumab)

Dosage Form and Route: Injection, for subcutaneous use

Application Type/Number: BLA 125526

Applicant: GlaxoSmithKline LLC

1 INTRODUCTION

On November 4, 2014, GlaxoSmithKline LLC, submitted for the Agency's review a Biologics License Application (BLA) for NUCALA (mepolizumab) for the proposed treatment of patients with severe eosinophilic asthma.

NUCALA (mepolizumab) has been developed as an add-on maintenance treatment for a subgroup of patients with severe asthma, namely patients with severe eosinophilic asthma. The proposed dose of 100 mg is administered subcutaneously every 4 weeks to patients 12 years of age and older. This submission represents the first BLA for NUCALA (mepolizumab). There are no currently licensed biological products in the United States that target IL5.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DARP) on December 1, 2014 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for NUCALA (mepolizumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft NUCALA (mepolizumab) PPI received on November 4, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 14, 2015.
- Draft NUCALA (mepolizumab) Prescribing Information (PI) received on November 4, 2014, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 14, 2015.

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

In our collaborative review of the PPI we have:

- 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)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

AMANPREET K SARAI
09/24/2015

ADEWALE A ADELEYE
09/24/2015

SHAWNA L HUTCHINS
09/24/2015

LASHAWN M GRIFFITHS
09/24/2015

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

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

Memorandum

Date: September 18, 2015

To: Nina Ton, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Senior Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Deputy Director, OPDP

Subject: BLA 125526
OPDP labeling comments for NUCALA (mepolizumab) for
subcutaneous use (Nucala)

In response to DPARP's consult request dated December 1, 2014, OPDP has reviewed the draft labeling (Package Insert [PI], and Carton/Container Labeling) for Nucala and offers the following comments.

OPDP's comments regarding the proposed Patient Package Insert (PPI) will be incorporated into a collaborative review by the Division of Medical Policy Programs (DMPP) and OPDP and will be provided under separate cover.

PI:

OPDP's comments on the PI are provided directly below and are based on the draft labeling titled "BLA 125526 FDA Labeling Edits August 31 2015.doc" (attached) that was provided via email from DPARP on September 14, 2015.

Carton/Container Labeling:

OPDP has reviewed the proposed carton and container labeling submitted by the applicant on September 15, 2015, (eCTD sequence # 0045) and located at the following:

- [\\cdsesub1\evsprod\bla125526\0045\m1\us\114-labeling\1141-draft\draft-100mglabel.pdf](#)
- [\\cdsesub1\evsprod\bla125526\0045\m1\us\114-labeling\1141-draft\draft-100mgsmpllabel.pdf](#)
- [\\cdsesub1\evsprod\bla125526\0045\m1\us\114-labeling\1141-draft\draft-100mgcarton.pdf](#)
- [\\cdsesub1\evsprod\bla125526\0045\m1\us\114-labeling\1141-draft\draft-100mgsmplcarton.pdf](#)

We have no comments at this time on the proposed carton and container labeling.

Thank you for your consult. If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
09/18/2015

LABEL AND LABELING REVIEW

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

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

Date of This Review:	June 25, 2015
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 125526
Product Name and Strength:	Nucala (Mepolizumab) Powder for Injection, 100 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	GlaxoSmithKline
Submission Date:	November 4, 2014
OSE RCM #:	2014-2450
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Kendra Worthy, PharmD

1 REASON FOR REVIEW

As part of the BLA review process for Nucala, DPARP requested that we review the proposed container labels, carton labeling, and Prescribing Information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

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

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
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 label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Mepolizumab is a monoclonal antibody and is not marketed; the original BLA is currently under review.

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

DMEPA finds the proposed container label, carton labeling, and prescribing information acceptable.

4 CONCLUSION

We conclude that the proposed container label, carton labeling, and prescribing information acceptable.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Nucala that GlaxoSmithKline submitted on November 4, 2014.

Table 2. Relevant Product Information for Nucala	
Initial Approval Date	N/A
Active Ingredient	Mepolizumab
Indication	Add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/ μ L at initiation of treatment or blood eosinophils greater than or equal to 300 cells/ μ L in the past 12 months
Route of Administration	Subcutaneous
Dosage Form	Powder for Injection
Strength	100 mg per vial
Dose and Frequency	100 mg administered subcutaneously once every 4 weeks
How Supplied	Sterile, preservative-free, lyophilized powder for reconstitution and SC injection in cartons of 1 single-use glass vial with a rubber stopper (not made with natural rubber latex) and a flip-off seal
Storage	Below 25°C (77°F). Do not freeze. Store in the original package to protect from light

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with postmarket medication error data, we reviewed the following Nucala labels and labeling submitted by GlaxoSmithKline on November 4, 2014.

- Container label
- Carton labeling
- Professional Sample label
- Professional Sample Carton Labeling

(b) (4)

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

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/s/

LISSA C OWENS
06/25/2015

KENDRA C WORTHY
06/26/2015

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: June 12, 2015

TO: Nina Ton, Pharm.D., Regulatory Project Manager
Sofia Chaudhry, M.D., Medical Officer
Lydia Gilbert-McClain, M.D., Deputy Division Director/Cross Discipline
Team Leader
Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

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

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

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

SUBJECT: Evaluation of Clinical Inspections

BLA: 125526

APPLICANT: GlaxoSmithKline

DRUG: mepolizumab

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATIONS: uncontrolled, (b) (4) asthma

CONSULTATION REQUEST DATE: December 30, 2014

INSPECTION SUMMARY GOAL DATE (original): July 10, 2015

INSPECTION SUMMARY GOAL DATE (revised): June 12, 2015

DIVISION ACTION GOAL DATE November 4, 2015

PDUFA DATE: November 4, 2015

I. BACKGROUND:

A strategy aimed specifically at eosinophilic inflammation may have particular benefit in patients with severe (b) (4) asthma and frequent exacerbations. High sputum eosinophil counts are associated with poor control and predict future exacerbations. Eosinophil recruitment and activation is promoted by IL-5. The proposed therapeutic biologic for uncontrolled, (b) (4) asthma, mepolizumab, is a humanized anti-IL-5 antibody (IgG1 kappa).

Two adequate and well-controlled clinical trials submitted in support of the applicant's BLA were selected for domestic clinical site inspections. One clinical site was selected for each study based on a large number of enrolled subjects.

Study MEA112997:

Study MEA112997 was a multicenter, randomized, placebo-controlled, double-blind, parallel group study. The primary study objective was to evaluate the dose response, based on efficacy and safety of three doses of intravenous (IV) mepolizumab (75 mg, 250 mg and 750 mg) compared to placebo over a 52-week treatment period in adult and adolescent subjects with severe uncontrolled refractory asthma. The primary efficacy endpoint was the frequency of clinically significant exacerbations of asthma as defined by a worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or Emergency Department visits.

Study MEA115588:

Study MEA115588 was a Phase 3, multicenter, randomized, placebo-controlled, double-dummy, double-blind, parallel group trial. The primary study objective was to evaluate the efficacy of mepolizumab 75 mg IV or 100 mg subcutaneous (SC) every 4 weeks versus placebo on the frequency of clinically significant exacerbations in adult and adolescent subjects with severe, uncontrolled, refractory asthma. The primary efficacy endpoint was the frequency of clinically significant exacerbations of asthma, as defined by a worsening of asthma which required use of systemic corticosteroids and/or hospitalization and/or Emergency Department (ED) visits.

II. RESULTS:

Name of CI Location	Study Site/Protocol/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Jeremy Cole, M.D. IPS Research Company 1111 North Lee, Suite 400 Oklahoma City, OK 73103	Site #067912 Protocol MEA112997 Subjects=10	March 2-5, 2015	NAI
Mark C. Liu, M.D. Asthma and Allergy Center Johns Hopkins Bayview Medical Center 5501 Hopkins Bayview Circle Baltimore, MD 21224	Site #099254 Protocol MEA115588 Subjects=9	January 28- February 4, 2015	NAI
Sponsor: GlaxoSmithKline. 5 Moore Drive P.O. Box 13398 Research Triangle Park, NC 27709	Protocols MEA112997and MEA115588	April 6-10, 2015	Preliminary NAI

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

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

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

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

CLINICAL STUDY SITE INVESTIGATOR

1. Jeremy Cole, M.D., Protocol MEA112997/Site #067912

Oklahoma City, OK

a. What was inspected:

The inspection was conducted from March 2 to 5, 2015. A total of 10 subjects were screened and enrolled. Nine subjects completed the study. An audit of ten enrolled subjects' records 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.

b. General observations/commentary:

Source documents for those enrolled subjects whose records were reviewed were verified against the case report forms and NDA 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 Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Mark C. Liu, M.D., Protocol MEA115588/ Site #099254

Baltimore, MD

a. What was inspected:

The inspection was conducted from January 28 to February 4, 2015. A total of 11 subjects were screened and 9 patients enrolled. Nine patients completed the study. An audit of 9 enrolled subjects' records 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.

b. General observations/commentary:

Source documents for those enrolled subjects whose records were reviewed were verified against the case report forms and NDA 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 Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR

3. GlaxoSmithKline.

Research Triangle Park, NC

a. What was inspected:

In accordance with the CDER BLA/NDA pre-approval, Sponsor/Monitor/CRO inspection program, using the Bioresearch Monitoring Compliance Program (CP 7348.810), an inspection of GSK was performed to review GSK's conduct of clinical studies in support of BLA 125526.

The inspection was conducted from April 6-10, 2015 with CDER OSI participation. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors. Additionally, GSK's blinding procedures related to these studies were reviewed.

b. General observations/commentary:

For Studies MEA112997 and Study MEA115588, the sponsor maintained adequate oversight of the clinical trials. Site monitoring was performed by GSK using a blinded and unblinded monitor and in general, was adequate. Sponsor blinding procedures were reviewed during inspection and appeared adequate. There was no evidence of under-reporting of adverse events.

A Form FDA 483 was not issued at the end of the sponsor inspection. The clinical studies adhered to Good Clinical Practice.

c. Assessment of data integrity:

The sponsor monitoring of sites appeared to be reliable for Studies MEA112997 and Study MEA115588. Data submitted by this sponsor appear acceptable in support of the requested indication

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two adequate and well-controlled clinical trials (MEA112997 and MEA115588) were submitted in support of the applicant's NDA. Two domestic clinical study sites (Dr. Cole and Dr. Liu) were selected for audit. The Sponsor (GlaxoSmithKline) was also inspected for this new BLA.

The classification for Drs. Cole and Liu is No Action Indicated (NAI). The preliminary classification the sponsor, GlaxoSmithKline, is NAI.

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

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

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

ANTHONY J ORENCIA
06/12/2015

JANICE K POHLMAN
06/12/2015

KASSA AYALEW
06/12/2015



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

Division of Pediatric and Maternal Health Memorandum

Date: June 8, 2015 **Date consulted:** December 19, 2014

From: Miriam Dinatale, D.O., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

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

Lynne P. Yao, MD, OND, Acting Division Director
Division of Pediatric and Maternal Health

To: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Drug: Nucala (mepolizumab) for injection for subcutaneous use

BLA: 125526

Applicant: GlaxoSmithKline LLC

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma

Materials Reviewed:

- DPMH consult request dated December 19, 2014, DARRTS Reference ID 36376529
- Sponsor's submitted background package for BLA 125526, mepolizumab

Consult Question:
DPARP requests DPMH assistance with pregnancy and lactation labeling to comply with the Pregnancy and Lactation Labeling Rule for a new BLA.

INTRODUCTION

Nucala (mepolizumab) is a humanized monoclonal antibody, immunoglobulin G1 kappa (IgG1 kappa) that targets human interleukin-5 (IL5).¹ On November 5, 2014, GlaxoSmithKline LLC submitted Biologics License Application (BLA 125526) to obtain approval to market Nucala for the proposed indication of the treatment of patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 300 cells/ μ l in the past 12 months.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) consulted the Division of Pediatric and Maternal Health (DPMH) on December 19, 2014 to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements and to provide comments to be included in the labeling that will be sent to the applicant.

BACKGROUND

Asthma

Asthma is a chronic inflammatory disease of the airways seen in 5-10% of adults and children and is well-controlled with inhaled therapy in most patients. Ten percent of asthma patients have disease that is severe, and of these patients, 30-40% use regular oral corticosteroids to control their asthma.²

Eosinophilic inflammation of airways plays a role in the pathogenesis of asthma, and an eosinophilic asthma phenotype has been identified. Eosinophilic asthma can be associated with increased asthma severity, atopy, late-onset disease, and steroid insensitivity. While most asthma patients can be controlled with step-wise treatment approaches, some asthma patients continue to be uncontrolled despite these treatment plans. Such patients may require treatments with high-dose inhaled corticosteroids and additional controller and/or systemic corticosteroids.³

Asthma in Pregnancy

Asthma is the most common chronic condition of pregnancy. In pregnancy, asthma prevalence ranges from 1-4%. Asthma-related morbidity and mortality rates in pregnant women are comparable to those in the general population with a mortality rate of 2.1 per 100,000 persons in the U.S. Although women with mild asthma are unlikely to have problems during pregnancy, patients with severe asthma are at a higher risk of having complications, which include preeclampsia, pregnancy-induced hypertension, uterine hemorrhage, preterm labor, premature birth, congenital anomalies, fetal growth restriction, and low birth weight, especially in the last trimester of pregnancy. Pregnant women with severe asthma are at risk for respiratory failure (requiring mechanical ventilation), barotrauma, and death.⁴

¹ Sponsor Packet: BLA 125526 for mepolizumab: Original submission

² Bel, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *The New England Journal of Medicine*. 2014; 371; 1189-1197.

³ Sponsor Packet: BLA 125526 for mepolizumab: Original submission

⁴ Medscape website: <http://emedicine.medscape.com/article/796274-overview>. Accessed 12/30/2014

Mepolizumab and Drug Characteristics

Mepolizumab is an IgG1 kappa monoclonal antibody (mAb) that binds to and inactivates IL5, which is a cytokine that recruits eosinophils from the bone marrow and promotes the persistence and activation of these cells.⁵ The proposed mechanism of action of mepolizumab is to inhibit eosinophilic inflammation and reduce the number of eosinophils in both sputum and blood, which may result in a reduction in asthma exacerbations and the need for treatment with systemic glucocorticoids.⁶

Pregnancy and Nursing Mothers Labeling

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”⁷ also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule⁸ format to include information about the risks and benefits of using these products during pregnancy and lactation.

The PLLR will take effect on June 30, 2015; however, at this time applicants may voluntarily convert labeling to PLLR format.

DISCUSSION

Nonclinical Experience

Animal reproduction studies have not shown adverse effects (fetal and infant death or adverse effects of fetal or infant development) in cynomolgus monkeys treated with mepolizumab throughout pregnancy (including organogenesis) at doses (b) (4) times the maximum recommended human dose (on an AUC basis with maternal intravenous doses up to 100 mg/kg once every 4 weeks. The reader is referred to the nonclinical review by Timothy Robison for further details.

Mepolizumab and Pregnancy

The applicant did not conduct studies with mepolizumab in pregnant women. A search of published literature for available human pregnancy data was performed to update the Pregnancy subsection of labeling for this BLA, and no studies were found.

⁵ Bel, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. The New England Journal of Medicine. 2014: 371; 1189-1197.

⁶ Ortega, et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. The New England Journal of Medicine. 2014: 317; 1198-1207.

⁷ *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

⁸ *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

There were 10 women who became pregnant while taking mepolizumab in Phase III clinical trials, and the outcomes are reviewed below. See appendix A for a complete list of outcomes.⁹

- Two patients had a spontaneous abortion
 - 40 year-old female on mepolizumab 75mg, had a spontaneous abortion 132 days after the first dose of mepolizumab at 5-6 weeks gestation. There were no fetal anomalies reported.
 - 42 year-old female on mepolizumab 100mg, had a spontaneous abortion 64 days after the first dose of mepolizumab at 5 weeks gestation. There were no fetal anomalies reported.
- One patient had a medical pregnancy termination
 - 42 year-old female on mepolizumab 750mg, had an induced abortion 236 days after the first dose of mepolizumab at 14 weeks gestation. The reason for the termination was not reported. There were no fetal anomalies reported.
- Seven live births
 - All infants were born full term and had no apparent congenital anomalies.

Although there are no studies or case reports with mepolizumab use in pregnant women, there were 10 pregnancies in mepolizumab clinical trials that have been reported. In these cases, there were two spontaneous abortions, one medical termination and seven normal pregnancies. All of the women who became pregnant were exposed to mepolizumab during preconception (ranging from 4-20 weeks before conception) or the first trimester of pregnancy. There was no known evidence of fetal malformations in the abortions, but the number of pregnant women exposed was small.

Monoclonal antibodies, such as mepolizumab, appear to be transported across the placenta with a smooth linear rise in fetal IgG starting as early as 13 weeks gestation (start of the second trimester of pregnancy). One study (Malek, *et al.*) demonstrated that there is a continuous rise in the level of IgG observed between 17 and 41 weeks gestation. Fetal levels of IgG were 5-10% of the maternal level between 17 and 22 weeks gestation, but exceeded the maternal level by three-fold at term.¹⁰ In another study (Garty, *et al.*), the blood from 34 fetuses was obtained by percutaneous umbilical blood sampling via amniocentesis and peripheral venous blood was drawn from the mothers at the time of the procedure. The authors showed that although all IgG subclasses cross the human placenta, their transport is not uniform. IgG1 and IgG4 are transported more efficiently than IgG2 and IgG3. Fetal IgG subclass concentrations are similar to maternal concentrations at 38 weeks gestation and on occasion, IgG concentrations may be higher than maternal concentrations at delivery.¹¹ Therefore, since monoclonal antibodies, such as mepolizumab, appear to cross the placenta in increasing amounts as pregnancy proceeds, it is possible that the effects of mepolizumab may be greater during the second and third trimester of pregnancy.

⁹ GlaxoSmithKline Information Request for Pregnancy Outcomes for Patients Exposed to Mepolizumab in Phase III Studies, May 8, 2015.

¹⁰ Malek, et al. *Ex vivo* human placenta models: transport of immunoglobulin G and its subclasses. *Vaccine* 2003;21:3362-4

¹¹ Garty *et al.* Placental Transfer of Immunoglobulin G Subclass. *Clinical and Diagnostic Laboratory Immunology*. 1994; 1 (6): 667-669.

In clinical trials performed in adult patients, there were no severe adverse events with mepolizumab. Adverse reactions seen in clinical trials included headaches, back pain, eczema, urinary tract infection, lower respiratory tract infection, pharyngitis, upper abdominal pain, pyrexia and nasal congestion.

The Applicant-proposed labeling recommends that mepolizumab (b) (4) DPMH agrees that the benefits and risks of NUCALA should be considered when prescribing NUCALA to a pregnant woman because there is insufficient information to make a clear assessment of risk.

Mepolizumab and Lactation

A search of published literature in the Drugs and Lactation Database (Lactmed)¹² and Pubmed for available human lactation data was performed to update the Lactation subsection of labeling for this application. Although there is no information on mepolizumab in published literature, animal studies have shown that mepolizumab is present in the milk of cynomolgus monkeys, and there were no adverse effects seen in infant monkeys.

In general, IgG is present in breast milk in small amounts; therefore, there is a hypothetical likelihood that mepolizumab, an IgG1 antibody, will be present in breast milk. Mepolizumab has a bioavailability ranging from 74-80% (when given subcutaneously in the arm in asthma patients) and is widely distributed in the body. Therefore, although mepolizumab has a low molecular weight MW¹³ (249 Daltons) and a long half-life (16-22 days), the drug appears to be deposited into maternal tissues and should not be in maternal circulation.¹⁴

The applicant recommends (b) (4); however, there is no evidence of significant harm if the infant is exposed to the drug. In clinical trials performed in adult patients, there were no severe adverse events with mepolizumab (see “Mepolizumab and Pregnancy” for details of adverse events seen), and there was no evidence of adverse events seen in infant monkeys exposed to mepolizumab via breast milk.

Although it is likely for the drug to be present in breast milk, no specific risks to the breastfed infant have been identified at this time. DPMH and the DPARP Nonclinical team agree that (b) (4) and the Lactation Risk Summary should include the following risk and benefit statement:

¹²The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>

¹³ Molecular weight (MW): drugs with a MW less than 800 Daltons are transferred to the milk compartment more readily than those with MWs greater than 800 Daltons

¹⁴ Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

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

Proposed Mepolizumab Pregnancy Surveillance Study Protocol

(b) (4)

The proposed mepolizumab pregnancy surveillance study, which is voluntarily being done by the applicant, (b) (4) and will expand the pregnancy cohort arm to include targeted recruitment of patients with severe asthma. Because mepolizumab has been shown to maintain lowered blood eosinophil levels even after 12 weeks from the last dose, the pregnancy surveillance study (b) (4)

Reviewers comment:

There is no post-marketing commitment or requirement for the applicant to perform the pregnancy registry. The proposed mepolizumab pregnancy surveillance study is voluntarily being done by the applicant. DPMH agrees with placement of the mepolizumab pregnancy surveillance study contact information in section 8.1 of labeling and recommends that the pregnancy surveillance study be made a part of a post-marketing commitment so that the FDA will be able to track the study progress and periodically review the pregnancy outcomes. Since mepolizumab is a monoclonal antibody and has the potential to be transmitted from the mother to the fetus, it is important to monitor for any adverse effects seen during pregnancy and to the developing fetus.

CONCLUSIONS

Nucala (mepolizumab) labeling has been updated to comply with the PLLR. A review of the published literature revealed no information with Nucala (mepolizumab) use in pregnant or lactating women. DPMH has the following recommendations for Nucala labeling:

- **Pregnancy, Section 8.1**

- The “Pregnancy” subsection of Nucala labeling was formatted in the PLLR format to include “Pregnancy Registry,” “Risk Summary,” “Clinical Considerations,” and “Data” subsections¹⁵.

¹⁵ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

- **Lactation, Section 8.2**

- The “Lactation” subsection of Nucala labeling was formatted in the PLLR format to include the “Risk Summary” subsection¹⁶.

RECOMMENDATIONS

- 1.) DPMH revised subsections 8.1 and 8.2 in Nucala (mepolizumab) labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.
- 2.) DPMH recommends that the mepolizumab pregnancy surveillance study be a post-marketing commitment so that the FDA may track the study progress and periodically review the pregnancy outcomes.

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to NUCALA during pregnancy. Healthcare providers can enroll patients or encourage patients to enroll themselves by calling 1-877-xxx-xxxx or visiting

(b) (4)

Risk Summary

(b) (4) to inform (b) (4) drug associated risk.

Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In (b) (4) pre-and post-natal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with administration of intravenous mepolizumab throughout pregnancy at doses that produced exposures up to approximately (b) (4) times the exposure at the maximum recommended human dose (MRHD) of 100 mg [see Data]. (b) (4)

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

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

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

¹⁶ Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

Data

Animal data

In a pre- and post-natal development study, pregnant cynomolgus monkeys received mepolizumab from gestation days 20 to 140 at doses that produced exposures up to approximately (b) (4) times that achieved with the MRHD (on an AUC basis with maternal intravenous doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers (b) (4) day 178 post-partum. Levels of mepolizumab in milk were (b) (4) of maternal serum concentration.

In a fertility, early embryonic and embryofetal development study, pregnant CD-1 mice received a (b) (4) antibody at an intravenous dose of 50 mg/kg once per week throughout gestation. The (b) (4) antibody was not teratogenic in mice.

Embryofetal development of IL-5 deficient mice has been reported to be generally unaffected relative to wild-type mice. (b) (4)

8.2 Lactation

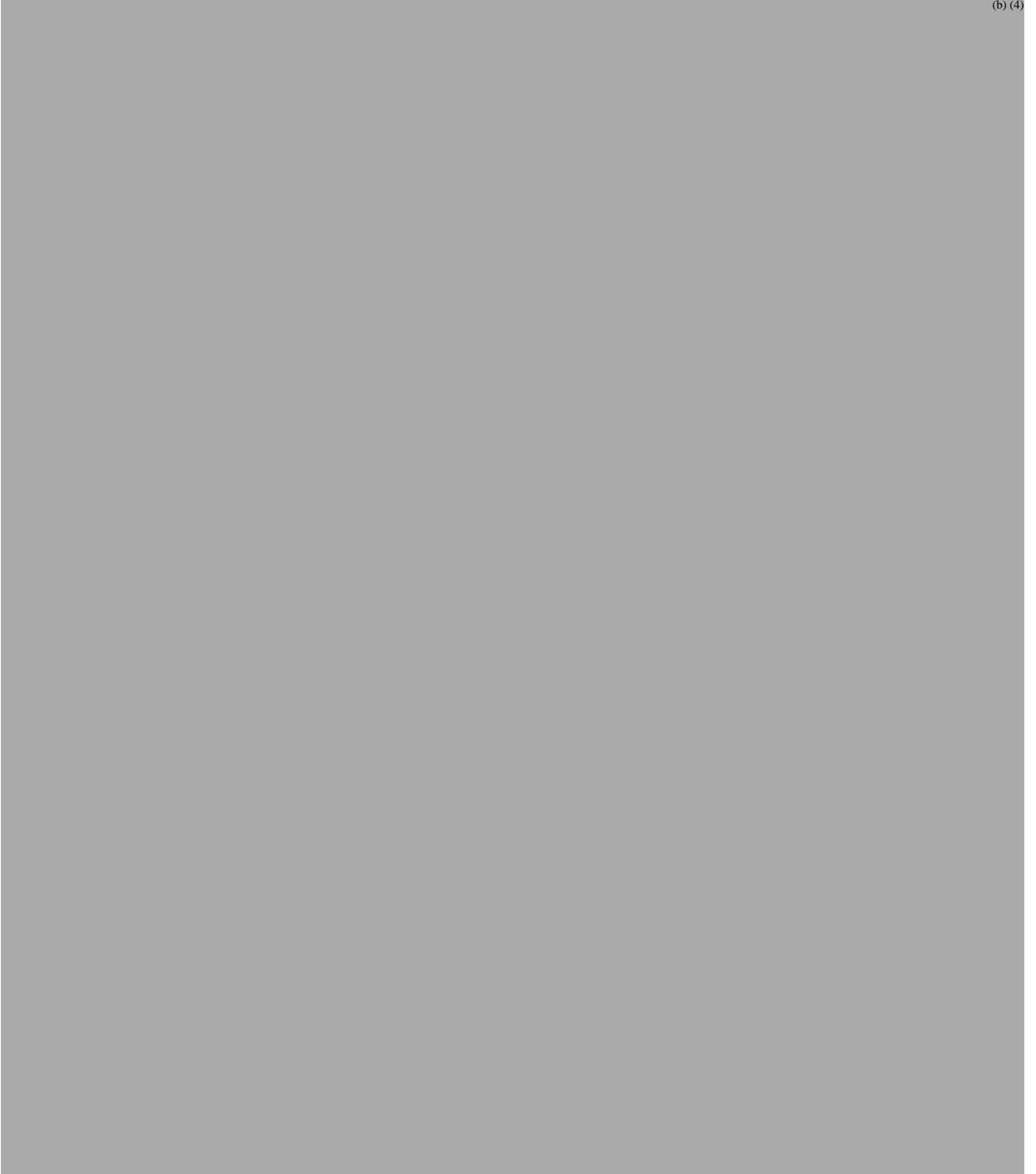
Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab is present in the milk of cynomolgus monkeys [see *Use in Specific Populations* (8.1)]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from NUCALA or from the underlying maternal condition.

(b) (4)

APPENDIX A – Applicant’s Proposed Nucala Pregnancy and Nursing Mothers Labeling

(b) (4)



(b) (4)

(b) (4)

Appendix B: GlaxoSmithKline Information Request for Pregnancy Outcomes for Patients Exposed to Mepolizumab in Phase III Studies

Table 1 Reports of Spontaneous Abortions Following Pregnancy Exposure in the Phase III Severe Asthma Studies

Case ID Age/ Gender	Study ID/ Subject ID	Event Preferred Term(s)	Study Drug/ Dose/ Time to Onset of Abortion from First Dose	Approximate Gestational Age at Abortion	Fetal Malformation
Z0005625A 27 Female ¹	112997 000022	Abortion Spontaneous, Exposure during Pregnancy	Placebo 127 days	10 weeks	Congenital anomaly ²
Z0007746A 40 Female ³	112997 000526	Abortion Spontaneous, Exposure during Pregnancy	Mepolizumab 75 mg 132 days	5-6 weeks ⁴	Not reported
Z0022160A 42 Female ⁵	115661 000231	Abortion Spontaneous	Mepolizumab 100 mg 64 days	4 weeks 5 days	No apparent congenital anomalies

1. Patient 022 had 3 previous pregnancies: 1 full term normal live birth, 1 spontaneous abortion, and one therapeutic abortion (no further details provided).
2. The investigator stated the event was a congenital anomaly; however, no additional details were provided.
3. Patient 526 had uterine myomas at the time of this event. She also had 2 previous spontaneous abortions.

Table 2 Reports of Induced Abortion Following Pregnancy Exposure in the Phase III Severe Asthma Studies

Case ID Age/ Gender	Study ID/ Subject ID	Event Preferred Term (s)	Study Drug/ Dose/ Time to Onset of Abortion from First Dose	Approximate Gestational Age at Abortion	Fetal Malformation	Reason for Termination
B0691977A 42 Female	112997 63	Abortion induced, Exposure during pregnancy	Mepolizumab 750 mg 236 days	14 weeks	No apparent congenital anomalies	Elective termination- No further details provided

Table 3 Reports of Live Births Following Pregnancy Exposure in the Phase III Severe Asthma Studies

Case ID Age/ Gender	Study ID/ Subject ID	Event Preferred Term (s)	Study Drug & Dose	Approximate Gestational Age at Birth	Pregnancy Complications	Delivery Complications	Delivery Type	Infant Birth Weight and Length	Apgar Scores (1,2,3)	Fetal Malformation
B0707435A Female	112997 00937	Exposure during pregnancy, Live Birth	Mepolizumab 75 mg	39 weeks	None reported	None reported	Cesarean	3990 g 54 cm	9, 9, U	No apparent congenital anomalies
B0955355A 17 Female	115588 1631	Exposure during pregnancy, Live Birth	Mepolizumab 75 mg	38 weeks 2 days	None reported	None reported	Vaginal	3200 g 51 cm	9, 10, U	No apparent congenital anomalies
B0939396A Female	115588 1782	Exposure during pregnancy, Live Birth	Mepolizumab 75 mg	39 weeks	None reported	None reported	Cesarean	2800 g 47.2 cm	7, 8, U	No apparent congenital anomalies
B1006144A Female	115661 001129	Exposure during pregnancy, Live Birth ¹	Mepolizumab 100 mg	39 weeks 1 day	None reported	None reported	Vaginal	4000 g 50.5 cm	9, 10, U	No apparent congenital anomalies
B0972897A 33 Female	115661 693	Exposure during pregnancy, Live Birth ¹	Mepolizumab 100 mg	39 weeks	None reported	None reported	Cesarean	Not reported	U, U, U	No apparent congenital anomalies
B0942353A 42 Female	115661 934	Exposure during pregnancy,	Mepolizumab 100 mg	38 weeks	None reported	None reported	Cesarean	2490 g Not reported	9, U, U	No apparent congenital anomalies

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

/s/

MIRIAM C DINATALE
06/08/2015

TAMARA N JOHNSON
06/08/2015

LINDA L LEWIS
06/08/2015

Signing as Acting Deputy Director, DPMH, on behalf of Dr. Lynne Yao, Acting Division Director,
DPMH

Consult
MEMORANDUM

*Department of Health and Human Services
Public Health Service
Food and Drug Administration*



DATE: April 23, 2015
RECEIVED: March 20, 2015
TO: Gregory Levin, Mathematical Statistician
CDER/OTS/OB/DBII
Nina Ton, PharmD, Regulatory Project Manager
CDER/OND/ODEII/DPARP
FROM: Yvonne Doswell, D.H.Sc., OIR/DIHD/HEMB
SUBJECT: CDER BLA125526, ICC1500180

Protocol Title Mepolizumab for treatment of severe asthma patients with high eosinophil levels
Drug Sponsor GlaxoSmithKline (GSK)
Drug Name Mepolizumab
Analyte Detected Eosinophil Count

I. BACKGROUND

GSK has submitted BLA 125526 to support the safety and effectiveness of mepolizumab for treatment of severe asthma patients with high eosinophil levels. The CDER review team is considering different ways to present efficacy results within subgroups defined by baseline eosinophil counts in Section 14 of labeling, and the inclusion of language about eosinophil levels in the actual indication is still very much up for debate. To help inform labeling considerations, it will be important to understand the analytical performance of assays used to measure eosinophils. We are requesting a review of the available evidence on the analytical performance characteristics (e.g., reference range, accuracy, precision) of platforms that measure blood eosinophil counts. This includes those used by the applicant in the key clinical trials supporting the safety and effectiveness of mepolizumab (MEA112997, MEA115588, MEA115575), in addition to any other assays typically used in clinical practice.

II. DEVICE USE IN THE TRIAL

The clinical studies MEA112997, MEA115588 and MEA115575 each employed the Coulter LH750 for eosinophil enumeration. Testing was performed in the (b) (4) central laboratory.

III. RESPONSE TO CDER QUESTIONS

CDER was advised to ask GlaxoSmithKline the following questions:

1. *Exact methodology used to perform eosinophil blood count (hematology platform).*

GSK Reply:

Studies MEA112997, MEA115588 and MEA115575 all utilized (b) (4) as the central laboratory. Sites were provided with a detailed laboratory manual with instructions for preparing all laboratory samples. Eosinophil blood counts were performed as part of the hematology (complete blood count) and differential sample. Two mLs of whole blood was drawn into lavender top EDTA tubes. Samples were shipped to (b) (4) at room temperature on the day of sample collection. This laboratory uses the Coulter LH750 which is widely used in the clinical laboratory industry. Automated differential analysis and classification are based on simultaneous measurement of cell volume, high frequency conductivity and laser light scatter. These measurements occur as the specimen is drawn through a very small aperture on the instrument as it rapidly measures the individual cells as they flow through. The aperture is large enough for one cell at a time to pass through. Thousands of cells are counted from each sample. Scatter plots as well as numeric values are then generated following this process.

2. *The reference ranges associated with interpretation of the eosinophil blood count test results (e.g. normal range and cut-point).*

GSK Reply:

In the United States, the absolute blood eosinophil count is reported in units of thousand cells per microliter (THOU/MCL). Outside of the United States the units were reported as GI/L. In all countries, the normal range was reported as 0.05-0.55 THOU/MCL or GI/L. This equates to 50 to 500 cells/ μ L.

3. *Samples types that are appropriate for patient testing using the methodology (e.g. purple top (EDTA) tube or whole Blood).*

GSK Reply:

The sample that is appropriate for analysis by the Coulter LH750, is a lavender top EDTA tube. A minimum of 1mL of whole blood is required for each sample to be analyzed.

4. *Actual samples types used for patient testing (e.g. capillary or venous)*

GSK Reply:

Venous blood was collected in Studies MEA112997, MEA115588, and MEA112997.

IV. CDRH COMMENTS TO CDER

The Coulter LH750 used by [REDACTED] ^{(b) (4)} in MEA112997, MEA115588, and MEA112997 was evaluated and subsequently cleared for in vitro diagnostic use under k011342. Beckman Coulter provided comprehensive in-house studies that utilized three LH 750 systems operating in either of two sample aspiration modes (open vial or closed vial), using both whole blood and prediluted whole blood. The analytical performance data submitted for the clearance of the Coulter LH750 included mode to mode comparison with predicate, within-run precision, paired-sample imprecision, carryover, linearity, accuracy, normal range, and nucleated red blood cell (NRBC) accuracy. In addition, comprehensive Hazard Analysis and software documentation information was provided.

Blood eosinophil counts are typically variable. There is limited data describing variability of blood eosinophil counts over time when used as a biomarker for asthma. Therefore, it is important to appreciate the limited utility of a single measurement for identification of patients with asthma. A normal blood sample measurement for eosinophils will show fewer than 350 eosinophil cells per microliter of blood. To establish the best cut-off value for eosinophil counts, the maximum sensitivity and specificity and efficiency of the hematology instrument to identify the presence of eosinophils should be established. If the eosinophil results for asthma patients fall outside of the analytical measuring range (AMR) of the test system, then the laboratory would need to conduct validation studies to establish AMR levels that extend beyond the manufacturer's specifications for measurement of eosinophil counts.

Depending on the analyzer characteristics, a patient specimen whose eosinophil test result is outside of the analytical measurement range a subsequent specimen dilution, concentration, or other pretreatment may be used to obtain a clinically reportable value.

Presently the following analytical performance characteristics are considered when evaluating hematology devices for the performance of complete blood counts (which includes eosinophil counts) for 510(k) clearance:

- Accuracy, precision and reproducibility
- Analytical Sensitivity/Specificity
- Normal Range/Abnormal Ranges- Confirmatory manual differentials recommended particularly at the low/high ends of the analytical measurement range (AMR)
- Limit Blank (LoB)/Limit of Detection (LoD)/Limit of Quantitation (LoQ)
- Device performance around the clinical cut-off and across the AMR of the device

The sponsor should demonstrate clinical validity which will require data from an appropriate (sufficiently powered) clinical study showing how eosinophil quantification reflects the clinical condition(s) for which the device is intended to be used.

In addition to recording the eosinophil values, demographic information (background characteristic variables) such as age, sex, race/ethnicity of patients should also be assessed when evaluating the eosinophil results. Please refer to “Clinical and Laboratory Standard Institute Reference Leukocyte (WBC) Differential Count (Proportional) and Evaluation of Instrumental Methods; Approved Standard”, CLSI H20-A2 for further recommendations.

Digital Signature Concurrence Table	
Reviewer Sign-Off	Yvonne T. Doswell -S 2015.04.23 13:36:15 -04'00'
Branch Chief Sign-Off	Claudia M. Dollins -S 2015.04.23 19:00:36 -04'00'
Division Sign-Off	Leonthena R. Carrington -A 2015.04.23 13:59:03 -04'00'

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

/s/

PHUONG N TON

04/24/2015

Administratively checked into DARRTS by Project Manager on behalf of the reviewer

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

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

Application: 125526

Application Type: New BLA

Name of Drug/Dosage Form: Nucala (Mepolizumab) 100 mg SC

Applicant: GlaxoSmithKline

Receipt Date: November 4, 2014

Goal Date: November 4, 2015

1. Regulatory History and Applicant's Main Proposals

GSK submitted a new biologic application for mepolizumab, a humanized monoclonal antibody (IgG1 kappa) indicated for add-on maintenance treatment in patients aged 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/ μ L. In this new application, the Sponsor submitted the prescribing information, patient information leaflet, and carton and container labels.

2. Review of the Prescribing Information

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

3. Conclusions/Recommendations

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

Appendix

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

Highlights

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

HIGHLIGHTS GENERAL FORMAT

Selected Requirements of Prescribing Information

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

Comment:

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

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

Selected Requirements of Prescribing Information

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

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

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

Comment:

Product Title in Highlights

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

Comment:

Initial U.S. Approval in Highlights

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

Comment:

Boxed Warning (BW) in Highlights

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

Comment:

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

Comment:

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

Comment:

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

Comment:

Selected Requirements of Prescribing Information

Recent Major Changes (RMC) in Highlights

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

Comment:

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

Comment:

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

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: "(Product) is a (name of established pharmacologic class) indicated for (indication)".

Comment:

Dosage Forms and Strengths in Highlights

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

Comment:

Contraindications in Highlights

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

Comment:

Adverse Reactions in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Patient Counseling Information Statement in Highlights

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

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

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

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

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

Comment:

Revision Date in Highlights

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

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

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

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

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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

Comment:

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

Comment:

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or

Selected Requirements of Prescribing Information

subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

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

Comment:

BOXED WARNING Section in the FPI

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

Comment:

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

Comment:

CONTRAINDICATIONS Section in the FPI

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

Comment:

ADVERSE REACTIONS Section in the FPI

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

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

Comment:

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

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

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

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

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

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

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

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

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

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

/s/

PHUONG N TON
01/05/2015

LADAN JAFARI
01/05/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

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

Application Information		
BLA# 125526	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"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Nucala Established/Proper Name: Mepolizumab Dosage Form: Lyophilized powder for injection Strengths: 100 mg		
Applicant: GlaxoSmithKline Agent for Applicant (if applicable):		
Date of Application: November 4, 2014 Date of Receipt: November 4, 2014 Date clock started after UN:		
PDUFA Goal Date: November 4, 2015		Action Goal Date (if different):
Filing Date: January 3, 2015		Date of Filing Meeting: December 18, 2014
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication: Treatment of patients with severe eosinophilic asthma		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input checked="" type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
<p>The application will be a priority review if:</p> <ul style="list-style-type: none"> • <i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i> • <i>The product is a Qualified Infectious Disease Product (QIDP)</i> • <i>A Tropical Disease Priority Review Voucher was submitted</i> • <i>A Pediatric Rare Disease Priority Review Voucher was submitted</i> 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<p>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</p>	

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

List referenced IND Number(s): 6971

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

questions below:					
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)]. 		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]? <p><i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i></p>		<input type="checkbox"/>	<input type="checkbox"/>		
<ul style="list-style-type: none"> Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <p>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p>		<input type="checkbox"/>	<input type="checkbox"/>		
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>					
Exclusivity		YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <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"/>	
NDAs/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"/>	

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

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

1

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

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

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

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

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

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

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Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <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 and date sent: PMHS sent 12/19/14</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment

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

End-of Phase 2 meeting(s)? Date(s): May 4, 2012 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): January 15, 2014 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 18, 2014

BACKGROUND: GSK submitted a new biologic application for mepolizumab dated November 4, 2014. The proposed indication is for the treatment of severe eosinophilic asthma in patients aged 12 years and older. The goal date is November 4, 2015.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nina Ton	Y
	CPMS/TL:	Ladan Jafari	N
Cross-Discipline Team Leader (CDTL)	Lydia Gilbert McClain		Y
Division Director/Deputy	Badrul Chowdhury		Y
	Lydia Gilbert McClain		Y
Office Director/Deputy	Curtis J. Rosebraugh		N
Clinical	Reviewer:	Sofia Chaudhry	Y
	TL:	Lydia Gilbert McClain	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Yunzhao Ren	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Bob Abugov	Y
	TL:	Greg Levin	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Tim Robison	Y
	TL:		
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) <i>(for protein/peptide products only)</i>	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Marjie Shapiro Jennifer Swisher	Y Y
	TL:		
Biopharmaceutics	Reviewer		
	TL:		
Quality Microbiology	Reviewer:	Reyes Candau Chacon Candace Gomez-Broughton	Y Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Jibril Abdus-Samad	Y
	TL:		
Facility Review/Inspection	Reviewer:	Christina Capacci-Daniel Laura Fontan	Y N
	TL:		
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Lissa Owens	Y
	TL:	Kendra Worthy	N
OSE/DRISK (REMS)	Reviewer:	Jasminder Kumar	Y
	TL:	Jamie Wilkins-Parker	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	Anthony Orenca	N
	TL:	Janice Pohlman	Y

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines Pharmacometrics	Reviewer:	Jerry Yu	Y
	TL:	Liang Zhao	Y
Other attendees	Sally Seymour, Ping Ji, Robert Pratt, Dipti Kalra, Eileen Wu, Efe Eworuke, Melinda Bauerlien		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</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 checked="" type="checkbox"/> YES Date if known: June 11, 2015 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CONTROLLED SUBSTANCE STAFF</p> <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIostatISTICS</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<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
Comments:	
IMMUNOGENICITY (protein/peptide products only)	<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
Comments:	
PRODUCT QUALITY (CMC)	<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
Comments:	
New Molecular Entity (NDAs only)	
<ul style="list-style-type: none"> Is the product an NME? 	<input 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> <p>If EA submitted, consulted to EA officer (OPS)?</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
<u>Quality Microbiology</u>	<input type="checkbox"/> Not Applicable
<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</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</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	
<p>Signatory Authority: Curtis J. Rosebraugh</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): 4/14/15</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input type="checkbox"/>	If priority review:

	<ul style="list-style-type: none"> • notify sponsor in writing by day 60 (see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAs completed: September 2014

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

/s/

PHUONG N TON
12/29/2014

LADAN JAFARI
12/29/2014