

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125526Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 125526 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DPARP PDUFA Goal Date: 11/4/15 Stamp Date: 11/4/2014

Proprietary Name: Nucala

Established/Generic Name: Mepolizumab

Dosage Form: 100 mg lyophilized powder for injection

Applicant/Sponsor: GSK

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
 - (2) _____
 - (3) _____
 - (4) _____
-

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Nucala is indicated for add-on maintenance treatment of asthma in patients with a history of exacerbations despite treatment with high-dose inhaled corticosteroids plus an additional controller with or without oral corticosteroids and applicable peripheral blood eosinophil counts.

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

- (a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*
- (b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 - No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input checked="" type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	<u>0</u> yr. __ mo.	<u>5</u> yr. <u>11</u> mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Are the indicated age ranges (above) based on weight (kg)? No; Yes.
- Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief**

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

justification):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input checked="" type="checkbox"/> Other	<u>6</u> yr. __ mo.	<u>11</u> yr. <u>11</u> mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	12 yr. __ mo.	17 yr. 11 mo.	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input checked="" type="checkbox"/>	Other	12 yr. __ mo.	17 yr. 11 mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

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pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	12 yr. __ mo.	17 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

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{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____**Q1:** Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

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proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

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
07/22/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # BLA # 125526	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Nucala Established/Proper Name: Mepolizumab Dosage Form: 100 mg Lyophilized Powder for Injection		Applicant: GSK Agent for Applicant (if applicable):
RPM: Nina Ton		Division: DPARP
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input checked="" type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>November 4, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: [CST SharePoint](#))

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> • Indicate what types (if any) of information were issued 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. 	<input type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 11/4/2015
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	<input type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) 	1/29/2015 1/23/2015
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input type="checkbox"/> None 1/5/2015 DMEPA: <input type="checkbox"/> None 9/25/2015, 6/26/2015 DMPP/PLT (DRISK): 9/24/2015, 8/7/2015 <input type="checkbox"/> None OPDP: <input type="checkbox"/> None 9/18/2015 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None 10/23/15 Other: <input checked="" type="checkbox"/> None 6/8/2015 DPMH Review
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	12/29/2014
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>8/5/2015</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)</p>	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	<p>11/4/15, 11/3/15, 10/29/15, 10/28/15, 10/8/15, 9/30/15, 9/17/15, 9/14/15, 9/8/15 (2), 8/31/15, 7/29/15, 7/9/15, 7/2/15, 6/28/15, 6/24/15, 6/22/15, 6/16/15, 6/4/15, 5/29/15, 5/27/15, 5/20/15, 5/15/15, 5/6/15, 5/1/15, 4/23/15, 4/21/15, 4/9/15, 3/25/15, 3/4/15, 2/25/15, 2/11/15, 1/16/15, 1/12/15 (2), 1/9/15, 12/31/14, 12/30/14, 12/12/14, 11/19/14, 11/14/14, 5/14/15, 8/19/15</p>
<ul style="list-style-type: none"> ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) 	
<ul style="list-style-type: none"> ❖ Minutes of Meetings 	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 1/15/2014
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 5/4/2012
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 4/28/2015
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 8/6/2015
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	<p>11/7/2012, 8/5/2014</p>

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	6/11/2015
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/4/2015
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 10/14/2015
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/23/2015
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 3
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	6/30/2015, 12/29/2014
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See page 16 and appendix (section 9.4) of medical officer review dated 6/30/2015
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>)	
• REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)	
• Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	<input type="checkbox"/> None 8/7/2015 No REMS recommended
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 6/12/2015, 5/29/2015, 5/20/2015
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 9/22/2015, 7/10/2015, 4/23/2015, 12/29/2014

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 7/10/2015, 7/5/2015, 12/30/2014
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 10/29/2015
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> No separate review 7/17/2015
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 9/20/2015, 6/29/2015, 12/16/2014
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i> Under Labeling Reviews/Other Reviews	<input type="checkbox"/> None 6/8/2015 DPMH - located under Labeling Reviews
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, pages 66-67
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/4/2015, 10/20/2015, 7/16/2015
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/4/2015, 7/9/2015, 12/31/2014
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None 10/15/2015 and 7/10/2015 Microbiology 4/10/2015 (2) CMC Stats
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See page 8 of CMC review dated 7/9/2015
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input type="checkbox"/> Done

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
11/04/2015

Ton, Phuong Nina

From: Ton, Phuong Nina
Sent: Wednesday, November 04, 2015 3:08 PM
To: 'Thomas Lampkin'
Subject: RE: BLA 125526 USPI - Labeling Comments

Tom,

Our team provided the table below. I confirm receipt of your draft revised label. Thank you.

Table 4. Percent OCS Reduction from Baseline for Subjects with ≤ 150 Eosinophils per mCL^a , Study 75 (courtesy of Dr. Robert Abugov)

Reduction in OCS	M100SC	Pbo	Odds Ratio (95% CI) ^b	Nominal P-Value ^b
90% - 100%	5 (29%)	0 (0%)		
75% - <90%	4 (24%)	0 (0%)		
50% - <75%	3 (18%)	2 (17%)		
>0% - <50%	1 (6%)	2 (17%)		
No change or any increase or lack of asthma control or withdrawal from treatment	4 (24%)	8 (67%)		
Statistical Analysis			6.7 (1.5, 29.0)	.008

^aAverage of values at baseline and screening.

^bConfidence limits and nominal p-values are from asymptotic theory and should be considered approximate.

Best Regards,
Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy,
and Rheumatology Products
OND/CDER/FDA
Phone: 301-796-1648
Email: phuong.ton@fda.hhs.gov

From: Thomas Lampkin [<mailto:Tom.A.Lampkin@gsk.com>]
Sent: Wednesday, November 04, 2015 2:54 PM
To: Ton, Phuong Nina
Subject: RE: BLA 125526 USPI - Labeling Comments

Hi Nina,

As discussed, we will accept the text as suggested since it is consistent with prior analyses we have performed. Because there are some differences and we do not have the analyses, would you please provide the results of the exploratory analyses. And we may need to follow-up to understand the methods in order to repeat the analyses.

So, no need for a teleconference.

Thank you.

Regards,
Tom

Tom Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
GlaxoSmithKline
Office: (919) 483-7783

From: Thomas Lampkin
Sent: Wednesday, November 04, 2015 2:30 PM
To: 'Ton, Phuong Nina'
Subject: RE: BLA 125526 USPI - Labeling Comments

Hi Nina,
I confirm receipt. We are working on right now. Trying to confirm some of the values.
Is there a possibility to have a teleconference?

Regards,
Tom

Tom Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
GlaxoSmithKline
Office: (919) 483-7783

From: Ton, Phuong Nina [<mailto:Phuong.Ton@fda.hhs.gov>]
Sent: Wednesday, November 04, 2015 1:12 PM
To: Thomas Lampkin
Subject: RE: BLA 125526 USPI - Labeling Comments

Tom,

Please find attached our labeling comments and confirm receipt. A Word version is also attached. We ask that you respond by 3 PM today. Thank you.

Best Regards,
Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy,
and Rheumatology Products
OND/CDER/FDA
Phone: 301-796-1648
Email: phuong.ton@fda.hhs.gov

From: Thomas Lampkin [<mailto:Tom.A.Lampkin@gsk.com>]
Sent: Wednesday, November 04, 2015 7:02 AM
To: Ton, Phuong Nina
Subject: RE: BLA 125526 USPI

Ok, thank you, Nina. I will be on the look-out.

Kind Regards,
Tom

Tom Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
GlaxoSmithKline
Office: (919) 483-7783

From: Ton, Phuong Nina [<mailto:Phuong.Ton@fda.hhs.gov>]
Sent: Wednesday, November 04, 2015 6:26 AM
To: Thomas Lampkin
Subject: RE: BLA 125526 USPI

Hi Tom,

We may have one additional change to Section 14 of the label regarding the exploratory analysis of Trial 75. I will send this to you as soon as possible.

Best Regards,
Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy,
and Rheumatology Products
OND/CDER/FDA
Phone: 301-796-1648
Email: phuong.ton@fda.hhs.gov

From: Thomas Lampkin [<mailto:Tom.A.Lampkin@gsk.com>]
Sent: Tuesday, November 03, 2015 1:43 PM
To: Ton, Phuong Nina
Subject: RE: BLA 125526 USPI

Hi Nina,
Thank you for the email. I confirm receipt.

Kind Regards,
Tom

Tom Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
GlaxoSmithKline
Office: (919) 483-7783

From: Ton, Phuong Nina [<mailto:Phuong.Ton@fda.hhs.gov>]
Sent: Tuesday, November 03, 2015 1:36 PM
To: Thomas Lampkin
Subject: RE: BLA 125526 USPI

Hi Tom,

Please see the attached labeling revisions from our team and confirm receipt. The Word document is attached.

Best Regards,

Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy,
and Rheumatology Products
OND/CDER/FDA
Phone: 301-796-1648
Email: phuong.ton@fda.hhs.gov

From: Thomas Lampkin [<mailto:Tom.A.Lampkin@gsk.com>]
Sent: Tuesday, November 03, 2015 9:09 AM
To: Ton, Phuong Nina
Subject: BLA 125526 USPI

Hi Nina,

I will await word from you on how and if any final clean-up of the draft USPI is needed.

When the final version of the USPI is available, would you please also provide as a Word document.

If you need to reach me today, the fastest way is either email or cell phone (b) (6).

Regards,
Tom

Thomas Lampkin, Pharm.D.
Senior Director, Therapeutic Group
US Therapeutic Groups
RD Chief Regulatory Office

GSK
5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States
Email Tom.A.Lampkin@gsk.com
Mobile (b) (6)
Tel +1 919 483 7783



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
11/04/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, and deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes to the BLA by 3:00 PM on November 4, 2015. In addition, please email me a courtesy copy of the revised label.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/November 4, 2015
Cleared by: MParks/November 4, 2015
 BAbugov/November 4, 2015
 RDavi/November 4, 2015
 TPermutt/November 4, 2015
 LJafari/November 4, 2015
Finalized by: NTon/November 4, 2015

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

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

/s/

PHUONG N TON
11/04/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, and deletions are in strike-out. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes to the BLA by the close of business on November 3, 2015. In addition, please email me a courtesy copy of the revised label.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/November 3, 2015
Cleared by: LGilbert-McClain/November 3, 2015
SChaudhry/November 3, 2015
TRobison/November 3, 3015
MDinatale/November 3, 2015
LJafari/November 3, 2015
Finalized by: NTon/November 3, 2015

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

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

/s/

PHUONG N TON
11/03/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

We also have the following comments:

1. According to 21 CFR 201.57(a)(7), the D&A Highlights must contain the critical dosage and administration information. Therefore, we recommend adding the following bullet to the D&A Highlights: "See Full Prescribing Information for instructions on reconstitution of lyophilized powder, and preparation and administration of the injection."
2. Change "^{(b) (4)} Limitations of Use" in I&U Highlights and FPI to "Limitations of Use."
3. Changes to Section 14 are ^{(b) (4)}
^{(u) (4)} is being described separately to highlight the lack of effect on lung function in the less severe asthma population studied.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes to the BLA by the close of business on November 2, 2015. In addition, please email me a courtesy copy of the revised label.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/October 28, 2015
Cleared by: LGilbert-McClain/October 28 and 29, 2015
MParks/October 28, 2015
LJafari/October 29, 2015
Finalized by: NTon/October 29, 2015

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/s/

PHUONG N TON
10/29/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information.

We are requesting your assistance in populating the attached tables for your New Molecular Entity, mepolizumab.

As part of FDASIA 2012, information on demographic subgroups in clinical trials for newly-approved drugs and biologics will be made publicly available on www.fda.gov/drugtrialssnapshot.

The website will include information on study design, results of efficacy and safety studies, and whether there were any differences in efficacy and side effects within sex, race, and age subgroups. The website is not intended to replace or replicate the package insert (PI), which is intended for health care practitioners, and will contain the following:

- Information written in consumer-friendly language
- “MORE INFORMATION” sections that provide more technical, data-heavy information
- Information that focuses on subgroup data and analyses
- Links to the PI for the product and to the FDA reviews at Drugs@FDA

With respect to the request for completion of the shell table for asthma exacerbation rate by subgroup, complete the table based on analyses in each of the studies or combinations of studies listed below, using the protocol specified primary efficacy analysis methods. For the individual studies estimate the treatment effect of mepolizumab relative to placebo within subgroups and test for the difference in overall treatment effect across subgroups. For combinations of studies, estimate the treatment effect of mepolizumab relative to placebo within subgroups and test for the difference in overall treatment effect across subgroups by combining the estimates from the individual studies inversely weighted by their variances. For all analyses, report least square means rather than raw means. Study numbers correspond to those used in section 14 of product labeling.

- Studies 2 and 3, each individually
- Studies 2 and 3, combined

With respect to the interaction tests of the treatment effect by race, for an individual study, the ANCOVA model should include the following factors/terms:

- race (as a categorical factor)

BLA 125526
Mepolizumab
GSK

- treatment
- treatment by race interaction term
- the covariates used in the primary analysis

When performing an interaction test of the treatment effect by race for a combination of studies, additionally include the following factors/terms:

- race by study interaction term
- treatment by study interaction term
- interaction terms with study for each covariate used in the primary analysis

Provide a forest plot for each set of subgroup analyses: studies 2 and 3 individually, and studies 2 and 3 combined. An example forest plot may be found at: <http://www.fda.gov/Drugs/InformationOnDrugs/ucm464098.htm> under the MORE INFO section of the question addressing whether there were any differences in how well the drug worked in clinical trials among sex, race and age.

Provide the code and a description of the statistical methods used to generate these analyses.

In order to facilitate the review of your submission, provide the requested information by November 2, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

Baseline Demographics for Pooled Efficacy Population for Trials 1-4 (N=1689)

Demographic Parameters	Trial 1 (N=362)	Trial 2 (N=616)	Trial 3 (N=576)	Trial 4 (N=135)	Pooled Trials 1-4 (N=1689)
Sex					
Men					
Women					
Age					
Mean years (SD)					
Median (years)					
Min, Max (years)					
Age Group					
ages 12-17					
18-64 years					
65 and above					
Race					
White					
Black or African American					
Asian					
American Indian or Alaska Native					
Native Hawaiian or Other Pacific Islander					
Other					
Region (populate according to the trial)					
United States					
Europe					
Asia					
Other					

Effect of Mepolizumab on Asthma Exacerbation Rate by Subgroup (see instructions above)

Demographic Parameters	MEPOLIZUMAB		CONTROL		Rate Ratio (95% Confidence Interval)	Test for Treatment by Subgroup Interaction (p-value)
	N	Mean Exacerbation Rate	N	Mean Exacerbation Rate		
Sex						insert
Male						
Female						
Age Group						insert
ages 12-17						
18-64 years						
65 and above						
Race						insert
White						
Black or African American						
Asian						
American Indian or Alaska Native						
Native Hawaiian or Other Pacific Islander						
Other						
Ethnicity						insert
Hispanic or Latino						
Not Hispanic or Latino						

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/October 28, 2015
Cleared by: NLowy/October 27 and 28, 2015
 LGilbert McClain/October 27, 2015
 SChaudhry/October 27, 2015
 LJafari/October 28, 2015
Finalized by: NTon/October 28, 2015

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/s/

PHUONG N TON
10/28/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014. We are providing our labeling comments and recommendations in the attached marked up labeling. The proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

We also have the following comments regarding Herpes Zoster:

The published scientific literature provides evidence that eosinophils can play a role in the antiviral host response. Human eosinophils constitutively express Toll-like receptor (TLR)-1, TLR-4, TLR-7, TLR-9, and TLR-10, all of which coordinate innate and acquired immune responses. Recognition of viral nucleic acids, including double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), and dsDNA, occurs by activation of TLR-3, TLR-7, and TLR-9, respectively, and can result in the production of type I interferons (IFNs) and the initiation of the antiviral host response. Further, eosinophils also express MHC-I and MHC-II, antiviral ribonucleases, cytokines, and chemokines, and can engage T cells, which supports the concept that this cell may contribute to the regulation of both innate and adaptive immunity. These cellular properties support a role for eosinophils in the antiviral host response.

We refer you to the following references:

1. Journal of Pediatrics 1992; 120: 28-32
2. Archives of Disease in Children 1994; 71:428-432
3. American Journal of Respiratory and Critical Care Medicine 1999; 159:1918-1924
4. American Journal of Respiratory and Critical Care Medicine 1994; 150:1646-1652
5. American Journal of Respiratory and Critical Care Medicine 2001; 164:109-116
6. Blood 2007; 110: 1578-1586
7. Clinical and Experimental Immunology 2006; 144: 409-417
8. Journal of Experimental Medicine 1999; 190: 1465-1478
9. Journal of Infectious Diseases 1998; 177: 1458-1464
10. Journal of Leukocyte Biology 2001; 70: 691-698
11. American Journal of Physiology 1997; 272: L512-L520
12. Journal of Virology 1998; 72: 4756-4764
13. Journal of Immunology 1998; 160: 1279-1284
14. Journal of Immunology 1998; 160: 4889-4895
15. American Journal of Respiratory and Critical Care Medicine 1998; 18: 675-686
16. Journal of Virology 2002; 76: 11425-11433
17. Journal of Experimental Medicine 2004; 200: 917-925
18. Journal of Virology 2010; 84: 8861-8870

Submit a clean copy and a tracked change version of the label incorporating our recommended changes to the BLA by the close of business on October 15, 2015. In addition, please email me a courtesy copy of the revised label.

BLA 125526
Mepolizumab
GSK

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager,
at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/October 7, 2015
Cleared by: LGilbert-McClain/October 7 and 8, 2015
SNabavian (for LJafari)/October 7, 2015
Finalized by: NTon/October 8, 2015

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/s/

PHUONG N TON
10/08/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information.

Provide, or point to the location in your submission of datasets containing observations collected to determine whether each patient in Study MEA115588 met enrollment criteria requiring historic peripheral counts of at least 300 eosinophils per microliter of blood in the past year. For each record, include a column indicating whether inclusion via historical blood eosinophil count was determined by interview with the patient, interview with the patient's physician, interview with the patient's family, or the use of laboratory records. Where laboratory records were used, include for each historical count the date of measurement, laboratory name, laboratory location, the measurement platform used, and the corresponding eosinophil count reference range.

In order to facilitate the review of your submission, provide the requested information by September 28, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/September 17, 2015
Cleared by: BAbugov/September 17, 2015
RDavi/September 16, 2015
LJafari/September 17, 2015
Finalized by: NTon/September 17, 2015

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/s/

PHUONG N TON
09/17/2015



BLA 125526

INFORMATION REQUEST

Glaxo/Smith/Kline
Attention: Thomas Lampkin, Pharm.D.
Senior Manager, Regulatory Affairs
Five Moore Drive
PO Box 13398
Research Triangle Park, NC 27709

Dear Dr. Lampkin:

Please refer to your original Biologics License Application received November 4, 2014, submitted under section 351(a) of the Public Health Service Act for mepolizumab 100 mg SC.

We are reviewing your submission and have the following comment. We request a written response in order to continue our evaluation of your application. Please submit your response by **September 21, 2015**.

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

1. In the information request sent to the sponsor on 04 Mar 2015 you were asked to justify the (b) (4) bioburden limit of (b) (4). Your justification for the (b) (4) bioburden of (b) (4) provided in Sequence 0016 is inadequate. Current industry practice is to set the (b) (4) limit to (b) (4) 100 mL. Establish the (b) (4) limits to (b) (4) 100 mL. In addition, (b) (4) samples should be collected (b) (4). Appropriate bioburden limits should be established for this (b) (4) sampling point based on manufacturing capability. As an interim measure the limits can be (b) (4) (b) (4). The establishment of limits should be made after data from a number batches is available (20-30). This may be implemented as a post-marketing commitment.



(b) (4)

If you have any questions, please contact me.

Sincerely,

Andrew Shiber -A

Digitally signed by Andrew Shiber -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Andrew Shiber -A,
0.9.2342.19200300.100.1.1=0014262141
Date: 2015.09.14 16:01:43 -04'00'

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014. We have the following comments regarding your proposed container labels and carton labeling submitted on August 13, 2015.

1. General Comments

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

2. Carton Labeling (trade and sample)

- a. 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.
- b. 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.

- c. On the rear panel, add the concentration of the reconstituted solution and deliverable volume with the reconstitution instructions.

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.

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. Add “No preservative” per 21 CFR 610.61(e).
- e. Add “No U.S. standard of potency” to appear on the bottom label per 21 CFR 610.61(r).
- f. 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

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.

3. Vial Container Label (trade and sample)

- a. 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.
- b. 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.
- c. Revise the storage information to read: “Store below 25°C (77°F) in original carton to protect from light. Do not freeze.”
- d. 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

In order to facilitate the review of your submission, provide the requested information and submit a clean copy and a tracked change version of the carton and container labels incorporating our recommended changes to the BLA by September 15, 2015.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/September 3, 2015
Cleared by: JAbdus-Samad/September 3, 2015
 LGilbert-McClain/September 8, 2015
 LJafari/September 8, 2015
Finalized by: NTon/September 8, 2015

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/s/

PHUONG N TON
09/08/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following request for information.

Provide your commitment to conduct the following pediatric studies and provide the final protocol submission date, study completion date and the final report submission date for each of the studies listed below.

PMR #1: Conduct 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)

Final protocol submission date: **Insert Date**
Study completion date: **Insert Date**
Final report submission date: **Insert Date (This date should be the same for both PMR#1 and PMR#2)**

PMR #2: Conduct a 12 month long-term safety and pharmacodynamics extension study of mepolizumab in pediatric patients with asthma 6 to 11 years of age (Part B of Study 200363)

Final protocol submission date: **Insert Date**
Study completion date: **Insert Date**
Final report submission date: **Insert Date (This date should be the same for both PMR#1 and PMR#2)**

In order to facilitate the review of your submission, provide the requested information by September 15, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/September 2, 2015
Cleared by: LGilbert-McClain/September 8, 2015
SSeymour/September 8, 2015
LJafari/September 2, 2015
Finalized by: NTon/September 8, 2015

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/s/

PHUONG N TON
09/08/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014. Attached are our revisions to your proposed package insert (PI). The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed. Of note, be advised that the Agency's decision to include a phrase regarding eosinophils as part of the indication statement is undergoing discussion within the Agency and a final determination has not yet been made.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes to the BLA by September 10, 2015. In addition, please send me a copy of the revised label via email.

If you have any questions, please contact Nina Ton, Senior Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/August 31, 2015
Cleared by: LGilbert-McClain/August 31, 2015
LJafari/August 31, 2015
Finalized by: NTon/August 31, 2015

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/s/

PHUONG N TON
08/31/2015

PeRC Meeting Minutes
August 5, 2015

PeRC Members Attending:

Linda Lewis
Gettie Audain
Rosemary Addy
Hari Cheryl Sachs
Robert "Skip" Nelson
Lily Mulugeta
Ruthanna Davi
Kevin Krudys
Thomas Smith
Belinda Hayes
Shrikant Pagay
Kristina Brugger

Non Responsive

Agenda

Non Responsive

10:20	BLA 125526	Nucala (mepolizumab) Partial Waiver/ Deferral /Plan/Assessment (with Agreed iPSP)	DPARP	Asthma
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Non Responsive

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immediately following this page

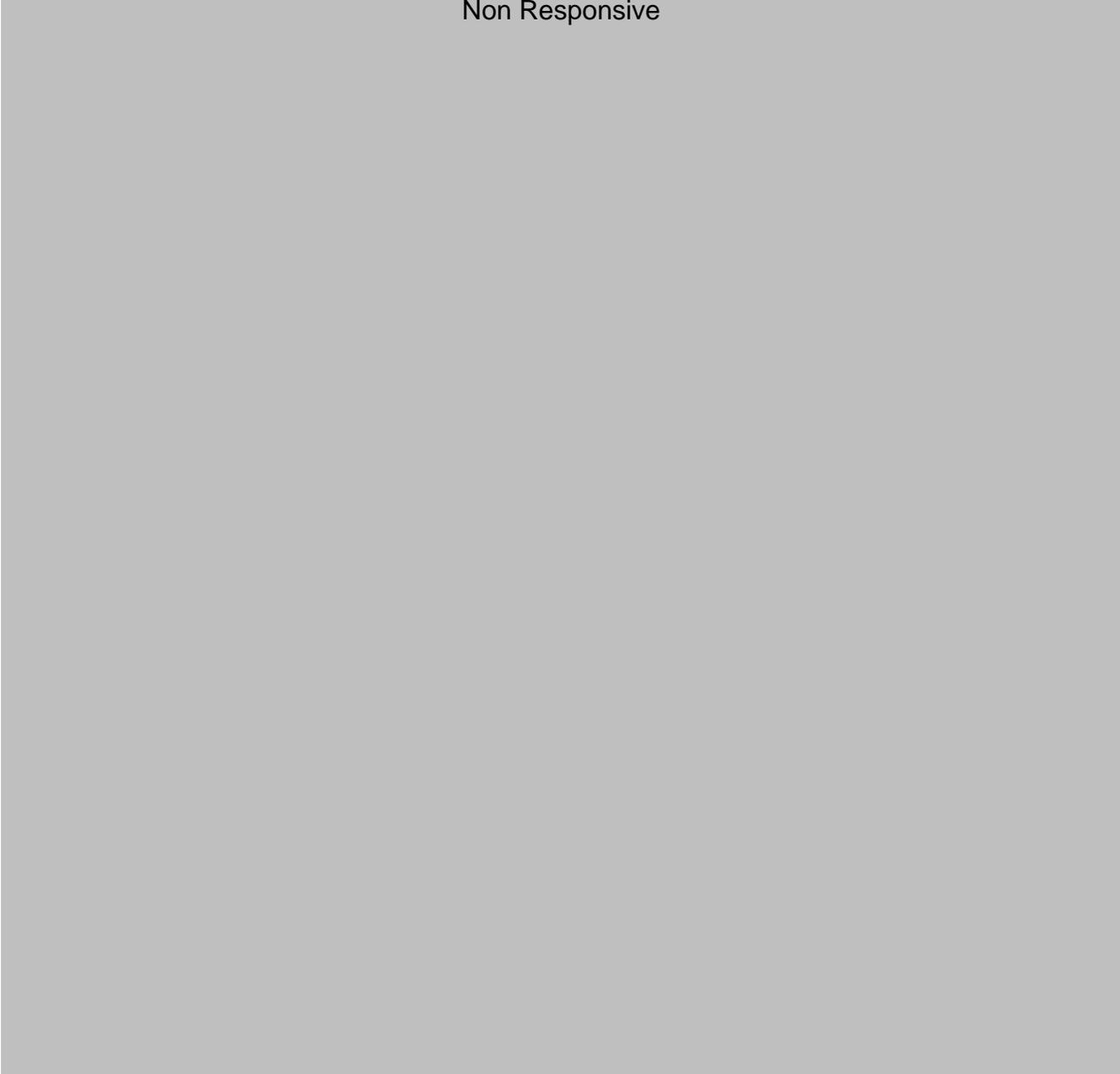
Non Responsive

Nucala (mepolizumab) Partial Waiver/Deferral/Plan/Assessment (w/Agreed iPSP)

- Proposed Indication: Severe asthma with eosinophilic inflammation
- The Division noted that adolescents were included in the studies intended to support the indication and efficacy was similar in adults and pediatric patients. Preliminary review of the data shows significant reduction in asthma exacerbations.
- A adverse events for this monoclonal antibody are similar to other approved asthma products. However,two cases of herpes zoster were confirmed in the adult studies. The sponsor has proposed language for the label that the will be negotiated when the marketing application is submitted.
- The Division agrees that [REDACTED] (b) (4)
- The Division also clarified they intend to issue PMCs for long-term safety data for this product. The PeRC agreed with this approach and also recommends that the Division consider issuing a WR.
- PeRC asked the Division to characterize the strength of the correlation between PK and the PD parameter, blood eosinophils. The Division clarified that degree of eosinophil count decrease is not directly correlated to clinical benefit.

- *PeRC Recommendations:*
 - The PeRC agreed with the plan for partial waiver in patients ages birth to 5 years, a deferral 6-11 years, and the assessment presented for patients 12-17 years of age.

Non Responsive



Non Responsive



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/s/

GEORGE E GREELEY
08/25/2015

Note: The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

Complete the section(s) of this template that are relevant to your *current submission*.

Definitions:

Deferral – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

Full Waiver – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

Partial Waiver – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

Pediatric Assessment – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

Pediatric Plan – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

Pediatric Population/Patient- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

PREA Pediatric Record/Pediatric Page – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

BACKGROUND	
Please check all that apply: <input type="checkbox"/> Full Waiver <input checked="" type="checkbox"/> Partial Waiver <input checked="" type="checkbox"/> Pediatric Assessment <input checked="" type="checkbox"/> Deferral/Pediatric Plan	
BLA/NDA#: 125526	
PRODUCT PROPRIETARY NAME: Nucala	ESTABLISHED/GENERIC NAME: Mepolizumab
APPLICANT/SPONSOR: GSK	
PREVIOUSLY APPROVED INDICATION/S:	
(1) _____	
(2) _____	
(3) _____	
(4) _____	
PROPOSED INDICATION/S:	
(1) <i>Asthma</i> _____	
(2) _____	
(3) _____	
(4) _____	
BLA/NDA STAMP DATE: November 4, 2014	
PDUFA GOAL DATE: November 4, 2015	
SUPPLEMENT TYPE:	
SUPPLEMENT NUMBER:	

Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?

Did the sponsor submit an Agreed iPSP? Yes No Submitted 5/15/2014

Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes No FDA Confirmed agreement 6/12/2014

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes No

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes No

If Yes, PMR # _____ NDA # _____

Does the division agree that this is a complete response to the PMR? Yes No

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.

WAIVER REQUEST

Please attach:

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived.
2. Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)
 - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
 - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
 - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
 - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (*This reason is for Partial Waivers Only*)

3. Provide justification for Waiver: Mepolizumab is a monoclonal antibody to interleukin 5 (IL-5) that prevents IL-5 from binding to its target receptor complex on the eosinophil cell surface resulting in a decreased peripheral blood and tissue eosinophils. As a specific anti-IL-5 monoclonal antibody, mepolizumab targets a highly select group of severe asthmatics who continue to have asthma exacerbations despite maximal standard care treatment including high dose inhaled corticosteroids plus an additional controller medication with or without oral corticosteroids and elevated blood eosinophil levels. According to the most recent CDC data the current asthma prevalence (2013) is 7.3% of the U.S population. The prevalence of asthma in children is reported to be 8.3% and 4.2% for the 0 – 4 year age group [http://www.cdc.gov/asthma/most_recent_data.htm]. It is estimated that severe asthma represents approximately 3-5% of adult asthmatics. In the pediatric population the prevalence of severe asthma is very low and reported with variable prevalence. The prevalence of severe asthma reported in the literature is for the overall severe asthma subset and does not take into account the highly selective group of severe asthmatics with eosinophilic inflammation (referred to in the academic community as “eosinophilic” asthma) that is the target of mepolizumab therapy. The prevalence of this subset of severe asthma is highly unlikely to occur in asthmatic patients < 6 years of age in sufficient numbers, thus making it impractical/not feasible to study subjects < 6 years of age with this asthma phenotype.

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor’s proposed language:

Specific labeling language is pending at this time, but the Division plans to add language summarizing the results for the adolescent population 12 – 17 years of age. The sponsor’s current language only states “the safety and efficacy in pediatric patients younger than 12 years have not been established.” We intend to keep this sponsor statement.

Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

basal cell and squamous cell skin cancer

bladder

breast

cervical

colorectal

endometrial

esophageal

cancer (continued):

follicular lymphoma

gastric

hairy cell leukemia

hepatocellular

indolent non-Hodgkin lymphoma

lung (small & non-small cell)

multiple myeloma

oropharynx (squamous cell)

ovarian (non-germ cell)

pancreatic

prostate

refractory advanced melanoma

renal cell

uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)
dry eye syndrome (keratoconjunctivitis sicca)
erectile dysfunction
essential thrombocytosis
Huntington's chorea
infertility & reproductive technology
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke
memory loss
menopause and perimenopausal disorders
mesothelioma
myelodysplasia
myelofibrosis & myeloproliferative disorders
osteoarthritis
overactive bladder
Parkinson's disease
paroxysmal nocturnal hemoglobinuria
plasma cells and antibody production disorders
polycythemia vera
postmenopausal osteoporosis
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis
reduction of thrombotic cardiovascular events in patients with coronary artery disease
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
retinal vein occlusions
stress urinary incontinence
temporary improvement in the appearance of caudal lines
treatment of incompetent great saphenous veins and varicosities
type 2 diabetic nephropathy
vascular dementia/vascular cognitive disorder/impairment

DEFERRAL REQUEST

Please attach:

Pediatric Record

1. Age groups included in the deferral request: 6 to 11 years old
2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)* A
 - a. Adult studies are completed and ready for approval
 - b. Additional safety or effectiveness data needed (**describe**)
 - c. Other (**specify**)
4. Provide projected date for the submission of the pediatric assessment (deferral date):
July 2017
5. Did applicant provide certification of grounds for deferring assessments? Yes No
6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time? Yes No
Study already submitted

SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency? Yes No
2. Does the division agree with the sponsor's plan? Yes No
3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion

and studies submitted)? Yes No

PK/PD trial in children 6 to 11 years of age

- a. **Protocol Submission:** *in-house (received January 6, 2015 ahead of estimated schedule of March 2015 in agreed upon PSP)*
- b. **Study Initiation date:** no later than June 2015
- c. **Estimated final Study report Submission:** No later than July 2017.

- 4. **Has a Written Request been issued?** Yes No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
- 5. **Has a PPSR been submitted?** Yes No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.

DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL

Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.

Nonclinical Studies:

No nonclinical studies

Clinical Studies:

PK PD study in children 6 to 11 years of age: (ongoing)

Age group and population (indication) in which study will be performed:

Between 6 and 11 years of age inclusive at the time of screening.

Approximately 40 male or female subjects with severe "eosinophilic" asthma aged 6 to 11 years inclusive at screening (Visit 1) to achieve

approximately 28 eligible subjects entering the treatment phase to allow availability of 20 evaluable subjects with a minimum of six subjects enrolled in the < 40 kg/body weight group.

Entry criteria:

Inclusion criteria

- Diagnosis of severe asthma, defined by the regional asthma guidelines (i.e. NIH, GINA etc.) for at least 12 months prior to Visit 1
- Eosinophilic airway inflammation that is related to asthma characterized as eosinophilic in nature as indicated by:
 - ✓ Elevated peripheral blood eosinophil count of ≥ 300 cells/uL demonstrated in the past 12 months OR
 - ✓ Elevated peripheral blood eosinophil count of ≥ 150 cells/ μ L at Visit 1
- A well-documented requirement for regular treatment with inhaled corticosteroid ($\geq 400\mu$ g/day fluticasone propionate (DPI) or equivalent daily) in the 12 months prior to Visit 1 with or without maintenance oral corticosteroids (OCS)
- Current treatment with an additional controller medication for at least 3 months or a documented failure in the past 12 months of an additional controller medication for at least 3 successive months (e.g. LABAs, theophylline, or leukotriene receptor antagonist)
- FEV1: Persistent airflow obstruction at either visit 1 or Visit 2
- Previously confirmed history of 2 or more exacerbations requiring treatment with systemic (oral, IM, or IV) corticosteroids in the 12 months prior to Visit 1, despite the use of high-dose ICS. For subjects receiving maintenance corticosteroids, the corticosteroid treatment for the exacerbation must have been a two-fold or greater increase in the dose.

Exclusion Criteria: Any history of life threatening asthma (e.g. requiring intubation), immunosuppressive medications, or immunodeficiency disorder, significant abnormality of rate, interval, conduction or rhythm in the 12-lead ECG, ALT and bilirubin > 2x ULN, parent/guardian with history of psychiatric disease, intellectual deficiency, substance abuse or other condition which will limit the validity of consent to participate in this study.

Clinical endpoints:

(b) (4)

Timing of assessments:

(b) (4)

Division comments on product safety:

Are there any safety concerns currently being assessed? Yes No

Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies? Yes No

Will a DSMB be required? Yes No

Other comments:

Division comments on product efficacy:

Mepolizumab is an anti-IL-5 monoclonal antibody that has demonstrated significant reduction in exacerbation in a highly selective sub-set of adult and adolescent asthmatics with severe asthma, who continue to have frequent exacerbations despite treatment with high dose ICS + additional controller medication, ± chronic systemic corticosteroids and have elevated peripheral blood eosinophil counts (related to asthma). Subjects on mepolizumab were able to reduce the amount of oral corticosteroids without loss of asthma control. Subjects treatment with mepolizumab showed clinically significant improvement in the SGRQ (St George's Respiratory Questionnaire) and the ACQ.

Division comments on sponsor proposal to satisfy PREA:

The sponsor proposes a waiver of PREA assessment in patients less than 6 years of age, and a deferral for subjects 6 to 11 years of age. Subjects 12 – 17 years of age were included in the adult asthma program and the sponsor considers the assessment for the 12 – 17 year olds complete. A total of 28 subjects were included in the adult program. For the 6 to 11 year old patients the sponsor proposes to screen 40 patients to have 28 eligible patients to study. The division believes that number of patients for each age group is reasonable as the patient population is a very selective subset of severe asthma patients. The prevalence of severe asthma (based on treatment with high dose ICS + one additional controller) in the pediatric population is very low and prevalence varies in the reported literature. A prevalence of 1.9% was reported for children ages less than 14 years of age from a UK General Practice Research database [*Prescribing patterns of asthma controller therapy for children in UK primary care: a cross-sectional observational study: BMC Pulmonary Medicine 201; 10:29R*]; This prevalence of severe asthma is without accounting for a subset of patients with airway eosinophilic inflammation which represents an even smaller number of patients. The sponsor's PK/PD approach to evaluate dose selection and collect safety and exploratory efficacy information in 6 to 11 year old patients appears adequate to satisfy PREA for this subset of severe asthma patients. Upon review by the pharmacometrics group, the number of 6 to 11 year old subjects in the PK/PD study should be adequate to derive precise estimates for PK and PD parameters based on population PK modeling and existing PK data. (b) (4)

. Thus we conclude that the PREA assessment for the adolescent population 12 – 17 years of age has

been completed and the PK/PD data for the 6 – 11 year old subjects should be adequate to satisfy PREA in this age group. Given the very limited population with this degree of asthma severity, we concur with the sponsor that a wavier should be granted for subjects < 6 years of age.

PeRC ASSESSMENT TEMPLATE

Please attach:

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

Date of PREA PMR:

Description of PREA PMR: *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC? **Yes** **No** If yes, did sponsor follow plan? Yes, the sponsor followed the plan

If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.

Indication(s) that were studied:

This section should list the indication(s) exactly as written in the *protocols*.

Example:

DRUG for the treatment of the signs and symptoms of disease x.

Number of Centers _____

Number and Names of Countries _____

Drug information:

Examples in italics

- **Route of administration:** *Oral*
- ***Formulation:** *disintegrating tablet*

- **Dosage:** 75 and 50 mg
- **Regimen:** list frequency of dosage administration

**If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

Types of Studies/ Study Design:

Example:

Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.

Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.

Age group and population in which study/ies was/were performed:

Example:

Study 1: patients aged X to Y years.

Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.

Number of patients studied or power of study achieved:

Example:

Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.

Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .

Entry criteria:

This section should list pertinent inclusion/exclusion criteria.

Example:

Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs

Patients had a negative pregnancy test if female.

Clinical endpoints:

Example:

Study 1: Clinical outcome and safety were the primary endpoints.

Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F

Statistical information (statistical analyses of the data performed):

This section should list the statistical tests conducted.

Example:

Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.

Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.

Timing of assessments:

Example:

Baseline, week 2, week 6, and end of treatment

Division comments and conclusions (Summary of Safety and Efficacy)

Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.

Specific language is pending at this time but the Division plans to add language summarizing the results for the adolescent population 12 – 17 years of age. The sponsor’s current language only states “the safety and efficacy in pediatric patients younger than 12 years have not been established.” We intend to keep this sponsor statement in addition to additional language summarizing the findings in the 12 to 17 year olds.

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/s/

PHUONG N TON
07/22/2015



BLA 125526

INFORMATION REQUEST

GlaxoSmithKline LLC
Attention: Thomas Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Lampkin:

Please refer to your Biologics License Application (BLA) dated November 4, 2014, received November 4, 2014, submitted under section 351(a) of the Public Health Service Act for Mepolizumab 100 mg SC.

We are reviewing your submission and have the following comments and information requests. We request a written response by July 17, 2015 in order to continue our evaluation of your application.

CMC Quality Microbiology

P.3.5.3 Process Validation Studies and Results

1. Provide actual hold times used in the microbiological hold time validation studies and the validated hold time.
2. With regard to the (b) (4) validation studies, provide the following:
 - a. Number of runs included in the validation studies.
 - b. Maximum (b) (4) used in the validation studies.
 - c. Maximum and minimum (b) (4) forces used in the validation studies.
 - d. Description of the controls used in the study.
 - e. Description of the quantitative dynamic dye test used to assess the integrity of the sealed vials, indicate if the method has been validated and submit the method validation report.
3. Indicate how (b) (4) validation parameters differ from those used during routine operations.
4. With regard to the (b) (4) validation studies, please provide the following.
 - a. Justification for using (b) (4)

- b. Report for the (b) (4) endotoxin challenge and (b) (4)
5. With regard to the (b) (4)
(b) (4) In addition, the validation should be relevant to equipment and components used in mepolizumab drug product manufacturing. Please submit the study reports which should include the following:
 - a. (b) (4)
 - b. (b) (4)
 - c. (b) (4)
 - d. (b) (4)
 - e. (b) (4)
 - f. (b) (4)
 6. Indicate if (b) (4) validation studies is used in mepolizumab manufacturing and provide the most recent requalification report.
 7. With regard to the lyophilizer (b) (4) validation studies, provide the following:
 - a. Clarify which lyophilizers are used in mepolizumab production.
 - b. Provide the study reports from initial qualification studies as well as most recent re-qualification using thermal and microbial challenge trials.
 8. With regard to the (b) (4)
(b) (4) s.
 9. Please provide the most recent (b) (4), number of rejections, deviations, and a summary of the environmental monitoring data.
 10. Please address the failed endotoxin recovery result of (b) (4)% in the DP spiking and hold study completed using CSE.

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Marjorie A.
Shapiro -S

Digitally signed by Marjorie A. Shapiro -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300081252,
cn=Marjorie A. Shapiro -S
Date: 2015.07.09 11:24:03 -04'00'

Marjorie Shapiro, Ph.D.
Team Lead
Division of Biotechnology Research and Review I
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014. Attached are our revisions to your proposed package insert (PI). The FDA-proposed insertions are underlined, deletions are in strike-out, and comments are included adjacent to the labeling text. Be advised that these labeling changes are not necessarily the Agency's final recommendations and that additional labeling changes may be forthcoming as the label is continued to be reviewed.

Submit a clean copy and a tracked change version of the label incorporating our recommended changes to the BLA by the July 24, 2015. In addition, please send me a copy of the revised label via email.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/July 2, 2015
Cleared by: TRobison/July 2, 2015
YRen/July 2, 2015
LJafari/July 2, 2015
Finalized by: NTon/July 2, 2015

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

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/s/

PHUONG N TON
07/02/2015

MEMORANDUM OF CORRESPONDENCE

DATE: 6/24/15

APPLICATION NUMBER: BLA 125526
DRUG PRODUCT: Mepolizumab 100 mg SC

BETWEEN:

Name: GlaxoSmithKline LLC

Alan Gardner, Ph.D., Director, Biopharmaceutical CMC RA
Alexandra Beumer Sassi, Ph.D., Regulatory Executive, Biopharmaceutical CMC RA
Narendra Bam, Ph.D., Vice President, Biopharmaceutical Development
Michael Byrne, Ph.D., Director, Biopharmaceutical Analytical Sciences
Bruce Fernie, Ph.D., Manager, Biopharmaceutical Analytical Sciences
Jennifer Dally, Manager, Biopharmaceutical Analytical Sciences
Don Espinosa, Analytical Scientist, Product Quality Center of Excellence
Rianna Gallo, Medicine and Process Delivery Manager
Robert Clemmitt, Ph.D., Medicine and Process Delivery Leader

AND

Name: Food and Drug Administration
Marjorie Shapiro, Ph.D., Team Lead, OBP, DBRR I
Jennifer Swisher, Ph.D., Quality Reviewer, OBP, DBRR I
Melinda Bauerlien, M.S., Senior Regulatory Business Process Manager, OPRO

Marjorie A.
Shapiro -S

 Digitally signed by Marjorie A. Shapiro 5
DN: c=US, o=U.S. Government, ou=HRH, ou=FDA
ou=People, o=9 2342 19200300 100 11=1300081252
cn=Marjorie A. Shapiro 5
Date: 2015.06.28 16:01:33 -0400

The Agency requested a teleconference with GSK to discuss concerns related to the IL5 neutralization potency assay. These include:

1. Inclusion of an upper limit for the release and EOSL specification
2. Satisfactory resolution of the method transfer to BioCTL that demonstrates the results are in line with the results from the transferring lab in Parma or a commitment to continue testing at Parma until the method performance at BioCTL matches that at Parma.

The sponsor submitted responses to the Agency's points in advance of the teleconference to aid the discussion.

1. Inclusion of an upper limit for the release and EOSL specification.

GSK Response:

GSK considers the proposal to maintain a (b) (4) limit acceptance criterion of ED50 ratio \geq (b) (4) for the IL5 neutralization bioassay appropriate to monitor biological activity. This was deemed appropriate based on knowledge of the mechanism of action of mepolizumab, statistical analysis of all available data, and inclusion of the stability indicating SPR method on the release and

stability specification. An upper limit for the assay is not needed; however, an upper control limit of ED₅₀ ratio of (b) (4) has been implemented to monitor assay performance.

Agency Response:

The Agency understands GSK's scientific rationale and is willing to accept not adding the upper limit for the release specification. The internal control limit of ED₅₀ ratio of (b) (4) will continue to be used and any result (b) (4) will be formally investigated.

2. Satisfactory resolution of the method transfer to BioCTL that demonstrates the results are in line with the results from the transferring lab in Parma or a commitment to continue testing at Parma until the method performance at BioCTL matches that at Parma.

GSK Response:

GSK considers that the IL5 neutralization analytical method transfer to the BioCTL was successful and has demonstrated that the results produced between the transferring (Parma) and receiving (BioCTL) test sites were comparable. It is the intent of GSK to continue the IL5 neutralization MDP2 release and MDP2/ (b) (4) stability testing at the BioCTL. This is based upon the following rationale which is discussed further in the subsequent text:

1. IL5 neutralization analytical method transfer results
2. Comparison of the IL5 neutralization process results between the BioCTL and historical test sites
3. Results and improvements from an on-going investigation into elevated ED₅₀ ratio values.

Agency Response:

The Agency finds the explanations regarding the shift in the assay results to be plausible, but without data demonstrating a resolution, continues to have concerns. For example, a result of an ED₅₀ ratio between (b) (4) obtained at BioCTL, could provide a result between (b) (4) at Parma and the lot would fail the test. GSK seems to be on the right track to solving the issues and should submit the results of the investigation when they are completed in the next month. If the Agency continues to have concerns after the new data are submitted, we will request another teleconference. If GSK does not hear from us, that is an indication that we are satisfied with the data and agree that the test can be performed at BioCTL with an acceptance criterion of ED₅₀ ratio of \geq (b) (4).

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following labeling comments.

Based on our review and the Advisory Committee discussion on June 11, 2015, we have determined that the submitted label requires substantial revisions.

In the attached document, we have outlined some of the necessary revisions with respect to content and organization of the product label, specifically for Sections 1, 6, 8, and 14. Use the outline provided to revise the product label as we have described. The outline provided is for the body of the package insert but corresponding changes should also be reflected in the Highlights section and Table of Contents. These comments are not all-inclusive and we may have additional comments based on the revised label.

In order to facilitate the review of your submission, provide the requested information by July 1, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA. If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

Section 1, Indications and Usage

- Revise the indication statement to remove the specific eosinophil threshold values. We are proposing the language noted below, although you may propose an alternative language for review.
 - Nucala is indicated for the add-on maintenance treatment of patients with asthma with a history of exacerbations despite treatment with high-dose inhaled corticosteroids plus an additional controller with or without oral corticosteroids, and guided by applicable peripheral blood eosinophil counts.

Section 8.4, Pediatric

- Final language to be determined. This section will need to be updated to reflect the available pediatric data from the development program.

Section 6, Adverse Reactions

- Section 6.1 Clinical Trials Experience in Asthma
 - Replace Table 1 with the frequency of common adverse events from the pooled database of the Study 75 + the first 24 weeks of Study 88. The corresponding text describing the studies and Table 1 should be updated to reflect this change.
 - A separate paragraph describing the long-term safety should follow. This section can include any new events meeting your frequency criteria from 52-week placebo-controlled Study 97 which are not included in Table 1. Any differences in the data from Study 97 or Study 88/75 from the long-term safety extensions can also be included here, if necessary.

Section 14, Clinical Studies

▪ Initial Paragraph:

- Include a description of study population for the severe asthma program and study designs for Study 06, 97, 88, and 75. To this section include a description of the eosinophil enrichment criteria used for Study 97 and Study 88/75. (b) (4)

- Include a table summarizing the demographics and baseline disease characteristics for each pivotal study. A sample table is provided below although you may propose alternative formatting for review.

	Study 06	Study 97	Study 88	Study 75
Mean age (yrs)				
Age 12 – 17, n (%)				
18 to 64, n (%)				
≥ 65, n (%)				
Female, n (%)				
Male, n (%)				
Caucasian, n (%)				
African Heritage, n (%)				
Asian, n (%)				
Other, n (%)				
Duration of Asthma, mean (yrs)				
Never Smoked, n (%)				
FEV1 at baseline				
Mean % predicated at baseline				
% reversibility				
Pre-SABA FEV1/FVC				
Post-SABA FEV1/FVC				
Mean eosinophil count at baseline (range)				
Exacerbation history, mean				
≥ 2 exacerbations/year				
≥ 3 exacerbations/year				

- **Section 14** (b) (4)
 - ◆ Include studies 97, 88, and 75.
 - ◆ (b) (4)
 - ◆ Summarize exacerbation results from Studies 97 and 88. Provide a tabulation of the primary efficacy results as well as results for ED visits + hospitalization, and hospitalization alone.
 - ◆ Provide a representative Kaplan-Meier Curve for Time to First Exacerbation for Study 88.
 - ◆ Provide a separate paragraph describing the results of Study 75, providing the results of the primary endpoint (in one or two sentences).
 - (b) (4)

▪ **Section 14^(b)₍₄₎ Lung Function Results**

- Include Studies 06, 97, 88, 75.
- Include a table that outlines the general patient population and difference from placebo in mean change from baseline in FEV1 at Weeks 12, 24, and 52. See the following example, although you may propose other formats for our review.

Trial	Patient population (<i>e.g. moderate asthma, severe asthma</i>)	Difference from placebo in mean change from baseline FEV1 at week 12 (95% CI)	Difference from placebo in mean change from baseline FEV1 at Week 24 (95% CI)	Difference from placebo in mean change from baseline FEV1 at week 52 (95% CI)
06				
97				
88				
75				

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/s/

SADAF NABAVIAN
06/24/2015

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information.

1. Provide analyses to delineate effects of mepolizumab compared to placebo for mean change from baseline of ACQ-5 in studies MEA11299797, MEA115588, and MEA115575. Provide means for each treatment arm, as well as the mean, p-value and confidence limit for each difference from placebo.
2. Provide analyses to delineate effects of mepolizumab compared to placebo for ACQ-5 percent response in studies MEA11299797, MEA115588, and MEA115575. Consider patients with an improvement at least 0.5 as responders. Provide response rate for each treatment arm, as well as the rate, p-value and confidence limit for each difference from placebo.
3. As in our information request of December 12, 2014, but for the analyses in 1 and 2 above, evaluate the percentage of data which is missing from the originally randomized population, and provide tipping point sensitivity analyses which vary assumptions about average values of the relevant endpoint among the patients on the mepolizumab and placebo arms who withdrew from the study early. Include the possibility that patients with missing data from the mepolizumab arms had worse outcomes than patients with missing data from the placebo arm. Ensure that documentation submitted with your report defines the distributions used to generate values for withdrawn patients and explains how those distributions were obtained.
4. Provide a set of analyses for SGRQ (where data is available) as in 1, 2, and 3 above. For the responder analyses, consider patients with an improvement of at least 4 as responders.
5. Provide the datasets and programs for 1, 2, 3, and 4 above. The analysis datasets should include a column or columns which clearly indicate whether each observation was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.
6. All eosinophil counts in your clinical development program were generated using a single measurement platform. To help guide patient selection, the USPI for mepolizumab will likely include those eosinophil counts to describe patient inclusion criteria and modification of treatment effects. Address the generalizability of the counts to clinical practice, where alternate measurement platforms are used with different reference ranges. One approach may be to compare counts obtained on your platform against other measurement platforms with a broad range of reference ranges as well as against manual counts. However, we acknowledge that other approaches to address this concern may be sufficient and/or preferable.
7. Provide an update regarding your plan to address the risk of parasitic disease with use of mepolizumab.

BLA 125526
Mepolizumab
GSK

In order to facilitate the review of your submission, provide the requested information by July 1, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/June 22, 2015
Cleared by: SChaudhry/June 22, 2015
LJafari/June 22, 2015
Finalized by: NTon/June 22, 2015

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/s/

PHUONG N TON
06/22/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following request for information.

Please complete the following table. Provide the calculation of ACQ7 if possible. We recognize the data may not have been captured appropriately to generate the ACQ-7 for the requested studies.

Study	Treatment	n	Baseline	Week 52, 32, 24	Δ baseline to week 52, 32, 24	Difference from placebo (95% CI)
ACQ including all 7 items – Complete ACQ						
97	Mepolizumab 75 mg IV Mepolizumab 250 mg IV Mepolizumab 750 IV Placebo					
88	Mepolizumab 100 mg SC Mepolizumab 75 mg IV Placebo					
75	Mepolizumab 100 mg SC Placebo					
ACQ including all 5 items – excludes bronchodilator use and FEV ₁						
97	Mepolizumab 75 mg IV Mepolizumab 250 mg IV Mepolizumab 750 IV Placebo	153 152 156 155				
88	Mepolizumab 100 mg SC Mepolizumab 75 mg IV Placebo	191 191 194				
75	Mepolizumab 100 mg SC Placebo	69 66				

BLA 125526
Mepolizumab
GSK

In order to facilitate the review of your submission, provide the requested information by June 23, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/June 16, 2015
Cleared by: SChaudhry/June 16, 2015
LJafari/June 16, 2015
Finalized by: NTon/June 16, 2015

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/s/

PHUONG N TON
06/16/2015



BLA 125526

INFORMATION REQUEST

GlaxoSmithKline LLC
Attention: Thomas Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Lampkin:

Please refer to your Biologics License Application (BLA) dated November 4, 2014, received November 4, 2014, submitted under section 351(a) of the Public Health Service Act for Mepolizumab 100 mg SC.

We are reviewing your submission and have the following comments and information requests. We request a written response by June 10, 2015 in order to continue our evaluation of your application.

Microbial Quality – Drug Substance

Indicate the status of the following pending requests and submit the required information to the BLA:

Question 7c, submitted on February 11, 2015: Repeat (b) (4) endotoxin qualification test using two additional batches. Amendment 0012 indicated that qualification of two additional batches of the (b) (4) would be completed by May 2015.

Question 7d, submitted on February 11, 2015 regarding Low Endotoxin Recovery studies. Amendment 0012 indicated that new studies using reference standard endotoxin (RSE) would be completed by March 2015.

Additional request:

1. Submit endotoxin limits for the (b) (4).
2. Include bioburden and endotoxin as part of the (b) (4)

Product Quality – Drug Product

3. Submit the IL5 neutralization transfer summary and provide an update into the investigation regarding the shift in assay performance upon transfer of the method to BioCTL. Finally,

indicate the lots in Figure 15 (Section 3.2.P.5.6 Justification of Specifications) that were tested at BioCTL or at the GMS Analytical Testing Laboratory in Parma.

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Marjorie A. Shapiro -S

Digitally signed by Marjorie A. Shapiro
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130008125
2, cn=Marjorie A. Shapiro -S
Date: 2015.06.04 08:31:51 -04'00'

Marjorie Shapiro, Ph.D.

Team Lead

Division of Biotechnology Research and Review I

Office of Biotechnology Products

Office of Pharmaceutical Quality

Center for Drug Evaluation and Research

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

Reference is made to your General Correspondence dated May 6, 2015, in which you requested advisory comments from the Office of Prescription Drug Promotion (OPDP). We have the following responses to your questions. Your questions are listed below in *italics* followed by our responses in normal font.

Question 1

Because the only representation of the product in the reconstitution video would be the vial of Nucala with no promotional messaging, would OPDP agree provision of the full prescribing information would suffice for communication of risk, without inclusion of Important Safety, since the video does not communicate any benefit statements?

FDA Response to Question 1

Based on the very early rendering of the video storyboard provided, this approach seems reasonable. However, determination of whether or not the proposed reconstitution video would need to be balanced with appropriate safety information will be a review issue.

In addition, we note your cover letter states the following:

In addition to access through the internet site, it is intended that representatives could refer to and/or show the video as part of the explanation of the product during a sales call. A copy of the full prescribing information would be provided during the sales call.

We remind you that any efficacy information provided by GSK representatives during a sales call must be balanced with appropriate safety information. Providing a copy of the full prescribing information during the sales call would not be sufficient to meet this requirement.

Question 2

Because USPI Section 2.1, Preparation and Administration, of the full prescribing information is unlikely to change once FDA provides comments on GSK's initial proposed labeling, would OPDP agree to review the reconstitution video against this version of the labeling, with a caveat that the video would have to be revised to incorporate any substantive future changes to this section of the labeling?

FDA Response to Question 2

We appreciate and understand your concerns regarding having OPDP's review of the reconstitution video secured prior to FDA approval of the application. We recommend reaching out to OPDP later in the review cycle, once labeling negotiations are substantially complete (generally after the labeling teleconference).

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/May 21, 2015
Cleared by: MFalter/May 20, 2015
 LJafari/May 27, 2015
 SChaudhry/May 27, 2015
 LGilbert McClain/May 27, 2015
Finalized by: NTon/May 27, 2015

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/s/

PHUONG N TON
05/27/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following request for information.

Check the numbers and provide the numbers noted in the attached table (Table 2. Selected Characteristics for patients in the relevant controlled clinical studies).

In order to facilitate the review of your submission, provide the requested information by noon Thursday, May 21, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

Table 1. Selected characteristics for patients in the relevant controlled clinical studies

	Study 06	Study 97	Study 88	Study 75
Demographics				
Age, mean in years	36	47	50	50
Asthma duration, mean in years	?	19	20	19
Percentage patients never smoked	70	78	72	82
Pulmonary function test				
Prebronchodilator FEV ₁ , mean % predicted	68	58	61	59
Prebroncodilator FEV ₁ /FVC ratio, mean	?	0.63	0.64	0.62
Reversibility, mean % ΔFEV ₁ post SABA	24	25	28	24
Eosinophil				
Baseline mean blood eosinophil count in μL	366	384	445	377
Exacerbation history				
Mean number of exacerbation in previous year	?	?	3.6	?
Percentage patients with ≥2 exacerbation in previous year	?	54	43	51
Background treatments during study				
Moderate dose inhaled corticosteroids (ICS)	Yes	-	-	-
High dose inhaled corticosteroids (ICS)	-	Yes	Yes	Yes
Non-ICS controller drug	-	Yes	Yes	Yes
Oral corticosteroids (OCS)	-	Yes & No	Yes & No	Yes & No

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/May 20, 2015
Cleared by: SChaudhry/May 20, 2015
LJafari/May 20, 2015
Finalized by: NTon/May 20, 2015

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/s/

PHUONG N TON
05/20/2015

BLA 125526
Mepolizumab
GSK

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information.

1. Provide the number of patients who failed screening for enrollment into Studies 97, 88 and 75 solely because they failed to meet the peripheral blood eosinophil criteria outlined in each study.
 - a. For Study 97, provide the number and percent of screened patients who failed to demonstrate a peripheral blood eosinophil count > 300 cells/ μ L, as well as the number and percent who failed to demonstrate a peripheral blood eosinophil count > 150 cells/ μ L .
 - b. For Studies 88 and 75, provide the number and percent of screened patients who failed to demonstrate a peripheral blood eosinophil count ≥ 150 cells/ μ L at screening, ≥ 300 cells/ μ in the past 12 months, and who failed both ≥ 150 cells/ μ L at screening and ≥ 300 cells/ μ L in the past 12 months.

In order to facilitate the review of your submission, provide the requested information by the close of business Wednesday, May 27, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/May 15, 2015
Cleared by: SChaudhry/May 15, 2015
 LGilbert McClain/May 15, 2015
 RDavi/May 15, 2015
 LJafari/May 15, 2015
Finalized by: NTon/May 15, 2015

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/s/

PHUONG N TON
05/15/2015



BLA 125526

MID-CYCLE COMMUNICATION

GlaxoSmithKline LLC
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Thomas Lampkin, PharmD
Senior Director, Global Regulatory Affairs

Dear Dr. Lampkin:

Please refer to your Biologic License Application (BLA) submitted under section 351(a) of the Public Health Service Act for mepolizumab.

We also refer to the teleconference between representatives of your firm and the FDA on April 28, 2015. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: April 28, 2015; 9:00 – 10:00 AM EST

Application Number: 125526
Product Name: Mepolizumab
Indication: Asthma
Applicant Name: GlaxoSmithKline

Meeting Chair: Badrul Chowdhury, MD, PhD
Meeting Recorder: Nina Ton, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, MD, Deputy Director, DPARP
Sofia Chaudhry, MD, Clinical Reviewer, DPARP
Ruthanna Davi, PhD, Deputy Director, Division of Biometrics II, Office of Biostatistics (OB)
David Petullo, MS, Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Robert Abugov, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Yunzhao Ren, PhD, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Nina Ton, PharmD, Regulatory Project Manager, DPARP

EASTERN RESEARCH GROUP ATTENDEES

Christopher A. Sese, Independent Assessor
Marc Goldstein, Independent Assessor

APPLICANT ATTENDEES

Steven Yancey, Vice President, Medicines Development Leader
Hector Ortega, Director, Physician Project Lead
Oliver Keene, Lead Project Statistician
Bhabita Mayer, Project Statistician
Stephanie Harris, Clinical Scientist
Robert Leadbetter, Lead Safety Physician
Deborah Templeton, Lead Safety Scientist
Isabelle Pouliquen, Clinical Pharmacologist
Tim Hart, Pre-Clinical Safety
JD Wilson, Non-Clinical Regulatory
Ilse Blumentals, CMC Regulatory

Stuart Hobbs, Labeling
Karen Miller, Global Regulatory Lead
Diana Daly, Vice President for Respiratory Therapeutic Group, Global Regulatory Affairs
Tom Lampkin, Senior Director, Regulatory

1. Introduction

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2. Significant Review Issues

- Concerns remain regarding the identification and labeling of the targeted patient population. In the absence of well-accepted clinical definition for “severe eosinophilic asthma” the appropriateness of including this term and the associated eosinophil thresholds in the indication statement will be one of the issues that will be discussed at the Advisory Committee Meeting.

Meeting Discussion

FDA commented that the use of the terminology “eosinophilic asthma” raised concerns since there is no guideline for this disease phenotype and deferred to the academic community to define the disease. FDA also noted that the enriched patient population would be best described in section 14 of the label and not in the indication statement.

- The available data for the adolescent population appears inadequate. Extrapolation of the indication to 12-17 year olds or the need for additional study will be a topic for discussion at the Advisory Committee Meeting. The committee will also be asked to discuss the appropriate pediatric age for further evaluation given the available efficacy and safety data.

Meeting Discussion

FDA reiterated that there is limited data in adolescent ages 12-17 as previously identified in the 74-day letter and noted this may result in a PREA PMR. GSK stated that they have additional analyses for the adolescent subgroup and can submit these for review. FDA agreed to review these addition analyses.

- The limited representation of minority groups in your program remains a concern. The adequacy of the program to be generalizable without inclusion of information in the product label will be a topic for discussion at the Advisory Committee Meeting.

Meeting Discussion

FDA advised GSK that this topic will be discussed at the Advisory Committee Meeting. It was noted that the term African Heritage may encompass subjects other than African-Americans. GSK stated they would provide additional subgroup analyses.

- Pending approval, a PMR to address use in parasitic disease is likely.

Meeting Discussion

FDA noted that this is an ongoing review issue.

- The program fails to provide replicate, significant improvements in SGRQ accounting for multiplicity. Inclusion in product labeling remains a review issue but appears unlikely to be supported.

Meeting Discussion

FDA commented that SGRQ is well used in COPD but not in asthma programs and asked GSK for a rationale to include it. GSK responded that SGRQ is a good tool that has been validated in all respiratory diseases including severe asthma and was used in Study 588 to characterize the patient population. FDA asked if this tool has been validated within the subtype of severe asthma referred to as “eosinophilic asthma” and GSK responded no. FDA concluded that SGRQ is unlikely to be included in the label, but it remains a review issue.

3. Major Safety Concerns

- No major safety concerns that would impact approvability have been identified at this time. However, the review of your application is on-going and an issue may still be identified.

Meeting Discussion

There was no discussion.

4. Risk Management Update

- We do not anticipate a REMS for this application at this time.

Meeting Discussion

There was no discussion.

5. Advisory Committee Meeting Plans

- An Advisory Committee Meeting to discuss this application is currently scheduled for June 11, 2015. Anticipated topics for discussion are outlined under Heading 3, Significant Review Issues.

Meeting Discussion

FDA noted that all review issues would be discussed at the Advisory Committee Meeting with the likely exception of parasitic disease.

6. Date and Format for Late-Cycle Meeting

- August 6, 2015; Teleconference

Meeting Discussion

There was no discussion.

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/s/

PHUONG N TON
05/14/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information.

With reference to the study entitled “Intravenous Study of Male and Female Fertility, Early Embryonic and Embryo-Fetal Development in CD-1 Mice (Study number: SB-240563/RSD-100P8V/1)”:

1. The incidence of cleft palate at the high dose of 50 mg/kg/week was increased (4 fetuses/2 litters; $1.90 \pm 1.33\%$). The concurrent control incidence was 1 fetus/1 litter ($0.28 \pm 0.28\%$). The published incidence of this finding is 0.17% (4/2352 fetuses) from Laboratory Animal Science 26 (2 Part 2): 293-300, 1976. Provide the historical control incidence (mean and range) of this finding from the testing laboratory over a 5-year period (e.g., 1995-2000) spanning the time when the study was conducted. In addition, provide a toxicological assessment of this finding.
2. Total resorptions were increased for females at 0.5 and 50 mg/kg/day, which might be attributed to higher incidences of late resorptions. Numbers of live fetuses were reduced for females at 0.5 and 50 mg/kg/week. We note the lack of dose-response relationships. Provide the historical control incidences (mean and range) of early, late, and total resorptions as well as live fetuses/dam from the testing laboratory over a 5-year period (e.g., 1995-2000) spanning the time when the study was conducted. In addition, provide toxicological assessments of these findings.

In order to facilitate the review of your submission, provide the requested information by 9:00 AM on Wednesday, May 13, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/May 6, 2015
Cleared by: TRobison/May 6, 2015
LJafari/May 6, 2015
Finalized by: NTon/May 6, 2015

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/s/

PHUONG N TON
05/06/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information regarding pregnancies noted during phase 3 trials with mepolizumab.

- If the patient had a spontaneous abortion, what was the gestational age at the time of the spontaneous abortion? Were there any fetal malformations?
- If the patient had a termination, what was the gestational age? Were there any fetal malformations? Why was the termination performed?
- If the patient had a live birth, were there any pregnancy complications? What was the gestational age at birth? Were there any maternal/infant complications at delivery? Was the delivery via c-section or vaginal delivery? What was the infant's birth weight, height, Apgar scores? Were there any fetal malformations noted?

In order to facilitate the review of your submission, provide the requested information May 8, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/April 30, 2015
Cleared by: MDinatale/April 30 and May 1, 2015
LJafari/April 30, 2015
Finalized by: NTon/May 1, 2015

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/s/

PHUONG N TON
05/01/2015

PDUFA V Program Mid-Cycle Communication Agenda

BLA 125526 Mepolizumab

**Teleconference
April 28, 2015
9:00 – 10:00 AM**

1. GSK/FDA Review Team/ERG Independent Assessor Introductions

2. Introductory Comments

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

3. Significant Review Issues

- Concerns remain regarding the identification and labeling of the targeted patient population. In the absence of well-accepted clinical definition for “severe eosinophilic asthma” the appropriateness of including this term and the associated eosinophil thresholds in the indication statement will be one of the issues that will be discussed at the Advisory Committee Meeting.
- The available data for the adolescent population appears inadequate. Extrapolation of the indication to 12-17 year olds or the need for additional study will be a topic for discussion at the Advisory Committee Meeting. The committee will also be asked to discuss the appropriate pediatric age for further evaluation given the available efficacy and safety data.
- The limited representation of minority groups in your program remains a concern. The adequacy of the program to be generalizable without inclusion of information in the product label will be a topic for discussion at the Advisory Committee Meeting.
- Pending approval, a PMR to address use in parasitic disease is likely.

- The program fails to provide replicate, significant improvements in SGRQ accounting for multiplicity. Inclusion in product labeling remains a review issue but appears unlikely to be supported.

4. Major Safety Concerns

- No major safety concerns that would impact approvability have been identified at this time. However, the review of your application is on-going and an issue may still be identified.

5. Risk Management Update

- We do not anticipate a REMS for this application at this time.

6. Advisory Committee Meeting Plans

- An Advisory Committee Meeting to discuss this application is currently scheduled for June 11, 2015. Anticipated topics for discussion are outlined under Heading 3, Significant Review Issues.

7. Date and Format for Late-Cycle Meeting

- August 6, 2015; Teleconference

Drafted by: SChaudhry/April 22 and 23, 2015
Cleared by: LGilbert McClain/April 22 and 23, 2015
LJafari/April 22, 2015
Finalized by: NTon/April 23, 2015

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/s/

PHUONG N TON
04/23/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information.

1. With reference to Study SB-240563/RSD-100P8V1 (Intravenous Study of Male and Female Fertility, Early Embryonic and Embryo-Fetal Development in CD-1- Mice), provide direct evidence (e.g., serum concentrations of SB-264091, lack of formation of anti-SB-264091 antibodies) or justification that male and female mice maintained exposure to SB-264091 throughout the dosing periods for each sex.
2. With reference to Study SB-240563/RSD-100X0L/2 (SB-240563: 6 Month Toxicity Study in Cynomolgus Monkeys), confirm that male and female monkeys in the study with an age range of 4 to 8.5 years were adults and that histopathological examinations of the reproductive organs meet the requirements for the fertility assessment per the ICH S6 (R1) Guidance.

In order to facilitate the review of your submission, provide the requested information by 9:00 AM on Thursday, April 30, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/April 21, 2015
Cleared by: TRobison/April 21, 2015
LJafari/April 21, 2015
Finalized by: NTon/April 21, 2015

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/s/

PHUONG N TON
04/21/2015



BLA 125526

INFORMATION REQUEST

GlaxoSmithKline LLC
Attention: Thomas Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Lampkin:

Please refer to your Biologics License Application (BLA) dated November 4, 2014, received November 4, 2014, submitted under section 351(a) of the Public Health Service Act for Mepolizumab 100 mg SC.

We are reviewing your submission and have the following comments and information requests. We request a written response by May 11, 2015 in order to continue our evaluation of your application.

1. Regarding Mepolizumab drug substance (DS) and drug product (DP) stability:
 - a. Provide updated stability data for (b) (4) and MPD2 lots.
 - b. In order to consider stability data from MDP1 lots to support a commercial shelf life for MDP2 lots, provide a scientific justification that explains why the MDP1 container closure configuration containing 250 mg mepolizumab per vial is representative of the MDP2 container closure configuration containing 100 mg mepolizumab per vial.

2. 3.2.P.2.3.3. Pharmaceutical Development: Lyophilization DOE and Commercial Scale studies. (b) (4) of lyophilized cake:
 - a. (b) (4)
 - b. (b) (4)
 - c. (b) (4)

[Redacted] (b) (4)

3. 3.2.P.2.3.4 Comparability assessment: Forced degradation studies of MDP1 vs MDP2. It is not clear if differences in some degradation rates between MDP1 and MDP2 can be explained as specific to the lots tested or if there are real differences between the MDP1 and MDP2 processes. Clarify if the MDP1 and MDP2 lots were treated at the same time and tested side-by-side. If they were tested side-by side, provide an explanation for the following observations:

[Redacted] (b) (4)

4.

[Redacted] (b) (4)

5.

6. 3.2.P.2.4.3 Container Closure System Extractables and Leachables: We note that studies were performed to assess the contribution of the bulk drug substance manufacturing process extractables that may be present in mepolizumab drug product, however it appears that specific leachables studies were not performed. Based on the extractables studies, you conclude that the extractables from the [Redacted] (b) (4) [Redacted] $\mu\text{g/day}$, do not pose a risk to patient safety. This may be a

reasonable conclusion, however, you did not provide direct evidence that the (b) (4) contributed to this results, only that you were unable to detect small molecules at a level (b) (4) µg/day. Provide additional information and/or a risk assessment that the (b) (4) contributing to this level of extractables are not a risk to patient safety similar to your approach for leachables from the drug product process described in 3.2.P.2.4.3.8.

7. (b) (4)

8. 3.2.P.3.5.3 Process Validation Studies Shipping Validation.

a. Tables 52 and 53 provide results of quality attribute testing from shipping studies. However, it is not clear which of the shipping studies outlined in Table 51 provided the vials that were tested.

b. On page 61 it states (b) (4)

(b) (4) Where is the temperature monitor placed (b) (4) and is this placement representative of the temperature and potential temperature excursions across all dimensions (b) (4)?

Microbial Quality – Drug Substance: Regarding Responses Submitted March 9, 2015 to the FDA Information Request Dated February 11, 2015

9. Your response to question 2.c is not clear. Please provide a diagram showing the bioburden sampling points with respect to (b) (4). Indicate maximum hold times in the diagram. Validation of maximum (b) (4) does not eliminate the need of bioburden sampling; however, (b) (4)

(b) (4) the bioburden sampling may be adequate.

10. (b) (4)

11. For your response to question 5.c, please submit summary results of maximum and minimum load from the simulated shipping studies (IOQ).

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

Marjorie A.
Shapiro -S

A red ribbon graphic is positioned vertically, overlapping the text 'Marjorie A.' and 'Shapiro -S'.

Digitally signed by Marjorie A.
Shapiro -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300
081252, cn=Marjorie A. Shapiro -S
Date: 2015.04.09 09:48:14 -04'00'

Marjorie Shapiro, Ph.D.
Team Lead
Division of Biotechnology Research and Review I
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information.

Provide the following information regarding the eosinophil blood count testing procedure used in your key clinical trials:

- Exact methodology used to perform eosinophil blood count (hematology platform)
- The reference ranges associated with interpretation of the eosinophil blood count test results (e.g. normal range and cut-point)
- Samples types that are appropriate for patient testing using the methodology (e.g. purple top (EDTA) tube or whole Blood)
- Actual samples types used for patient testing (e.g. capillary or venous)

In order to facilitate the review of your submission, provide the requested information no later than the close of business Wednesday, April 1, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/March 25, 2015
Cleared by: YDoswell (CDRH)/March 24 and 25, 2015
GLEvin/March 24, 2015
LJafari/March 25, 2015
Finalized by: NTon/March 25, 2015

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/s/

PHUONG N TON
03/25/2015



BLA 125526

INFORMATION REQUEST

GlaxoSmithKline LLC
Attention: Thomas Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Lampkin:

Please refer to your Biologics License Application (BLA) dated November 4, 2014, received November 4, 2014, submitted under section 351(a) of the Public Health Service Act for Mepolizumab 100 mg SC.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your application.

1.



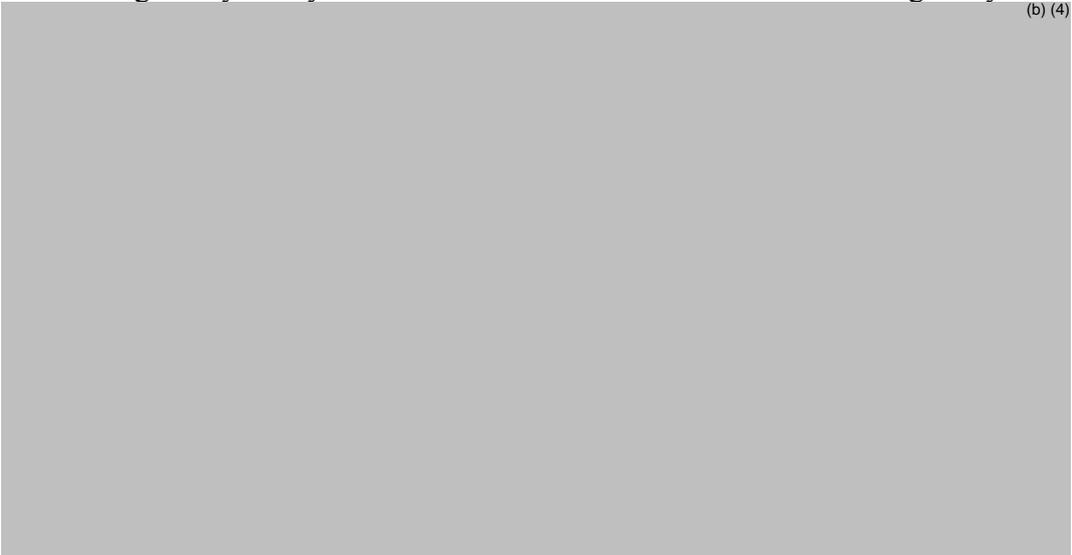
2.



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(CCI/tS) immediately following this page



13. S.5.3.1.4 Immunogenicity Assays: G6 electrochemiluminescent ADA screening assay:

- a.  (b) (4)
- b. 
- c. 
- d. 
- e. Regarding the studies to examine and overcome IL5 interference in the G6 MSD ADA assay: Although the integrated summaries of immunogenicity provide limited data regarding the behavior of IL5 in the MSD ADA assay, no formal investigation of IL5 tolerance of the MSD ADA assay has been included in the validation reports. Provide data regarding the behavior of the assay in the presence of IL5 concentrations that cover the clinically relevant range.

14. S.5.3.1.4 Immunogenicity Assays:  (b) (4) Assay to Detect Neutralizing Antibodies:

- a. Regarding sensitivity and drug tolerance: The poor sensitivity of your assay suggests that it may not be able to detect neutralizing antibodies at the low titer

value seen in most patients that have been confirmed positive for ADA. In addition, the substantial drug interference renders this assay even less likely to detect neutralizing antibodies in patients who have been exposed to multiple doses of mepolizumab, even at the proposed time of sampling. In keeping with this, the only patient that was identified as positive for neutralizing antibodies against mepolizumab had a much higher antibody titer than nearly all other

(b) (4)



15. S.5.3.1.4 Immunogenicity Assays: Screening and Neutralizing Assays:

(b) (4)



If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.
Team Lead
Division of Biotechnology Research and Review I
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

MARJORIE A SHAPIRO
03/04/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information:

1. For Studies MEA 112997, MEA115588, and MEA115575, provide a tabulation of the primary endpoint for each treatment group by age including subjects ages 12 to 17, 18 to 64, and ≥ 65 years of age, and < 40 and ≥ 40 years of age. Provide the data for the individual studies for each treatment group using the ITT population (mITT for Study 88).
2. For Studies MEA112997, MEA115588, and MEA115575, provide a tabulation of the primary endpoints for each treatment group by race and ethnicity. Include the following categories: White, Asian, African American/African Heritage, American Indian or Alaskan Native, Hawaiian/Pacific Islander and Other (e.g., mixed race), Not Hispanic/Latino and Hispanic/Latino. Provide the data for the individual studies for each treatment group using the ITT population (mITT for Study 88).
3. For Studies MEA112997, MEA115588, and MEA115575, provide a tabulation of the primary endpoints for each treatment group by region. Include the following categories: North America, European Union, and Rest of the world. Provide the data for the individual studies for each treatment group using the ITT population (mITT for Study 88).

In order to facilitate the review of your submission, provide the requested information no later than the close of business Wednesday, March 4, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/February 25, 2015
Cleared by: SChaudhry/February 25, 2015
 LGilbert McClain/February 25, 2015
 LJafari/February 25, 2015
Finalized by: NTon/February 25, 2015

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/s/

PHUONG N TON
02/25/2015



BLA 125526

INFORMATION REQUEST

GlaxoSmithKline LLC
Attention: Thomas Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Lampkin:

Please refer to your
Biologics License Application (sBLA) dated November 4, 2014, received November 4, 2014,
submitted under section 351(a) of the Public Health Service Act for Mepolizumab 100 mg SC.

We are reviewing your submission and have the following comments and information requests.
We request a written response by March 9, 2015 in order to continue our evaluation of your
application.

1. Description of the Manufacturing Process and Process Controls (3.2.S.2.2)

(b) (4)





5. Process Validation and/or Evaluation – Shipping Validation (3.2.S.5.3)

- a. Indicate the external temperature during the real time shipping validation study.
- b. Indicate if the location of the data-loggers for the maximum load study during the simulated shipping is the same as indicated in Figure 73 of section 3.2.S.2.5.
- c. Justify not using a minimum load for the real-life shipping validation study.

6. Control of Drug Substance – Analytical Procedures (3.2.S.4.2)

- a. Describe the bioburden and endotoxin methods for DS release, (b) (4) bulk (only bioburden), (b) (4) samples. Include sample volume, dilution factor if applicable, and bioburden sample incubation conditions.
- b. Clarify if the reported bioburden in the CofA result will be the sum of the (b) (4) and will be specified as such.

7. Control of Drug Substance – Validation of Analytical Procedures (3.2.S.4.3)

(b) (4)

8. Control of Drug Substance – Batch Analyses (3.2.S.4.4)

Clarify if endotoxin release result of batch T0414005 (endotoxin < (b) (4) EU/mg) shown in Table 2 of section 3.2.S.4.4 is a typo and amend the table in the BLA.

9. Control of Drug Substance – Batch Analyses Justification of Specification (3.2.S.4.5)

- a. Clarify if a release acceptance criterion is (b) (4)
- b. Unprocessed bulk specification should be changed from \leq (b) (4) to $<$ (b) (4).

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.
Team Lead
Division of Biotechnology Research and Review I
Office of Biotechnology Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

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/s/

MARJORIE A SHAPIRO
02/11/2015



BLA 125526

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

GlaxoSmithKline LLC
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

ATTENTION: Thomas Lampkin, PharmD
Senior Director Global Regulatory Affairs

Dear Dr. Lampkin:

Please refer to your Biologics License Application (BLA) dated and received November 4, 2014, submitted under section 351(a) of the Public Health Service Act for Mepolizumab, 100 mg per vial.

We also refer to:

- Your correspondence, dated and received November 7, 2014, requesting review of your proposed proprietary name, Nucala
- Your amendment to the Request for Proprietary Name Review, dated and received November 19, 2014

We have completed our review of the proposed proprietary name, Nucala, and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your November 7, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nichelle Rashid, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3904. For any other information regarding this application, contact Phuong (Nina) Ton, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
01/29/2015

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information:

1. Provide a tabulation of the pooled adverse events for trial MEA115575 and the first 24 weeks of trial MEA115588 for the placebo and mepolizumab 100 mg SC treatment arms. Highlight events that occur in $\geq 3\%$ of either treatment group and more commonly in the mepolizumab 100 mg SC arm than placebo.
2. Reconcile the numeric differences between the number of events in the “Any Event” rows and the individual PTs for Tables 2.102 and 2.105.
3. Provide an exposure adjusted analysis for the cardiac, vascular, thromboembolic and ischemic SAEs you identified in Tables 22, 2.102 and 2.105 of your ISS.
4. Tabulate the mean difference between treatments, and associated 90% and 95% confidence intervals, for the number of person years/event and events per person year for the cardiac SOC using the PCSA database as well as the cardiac/vascular/thromboembolic/ischemic SAEs you identified in Table 22 of your ISS. For these events, perform an additional model-based analyses that account for the time each patient is receiving a particular treatment (e.g. Poisson or Cox models) and which, for the integrated analyses, appropriately account for study differences^[1], either by adjusting for study in a model or carrying out meta-analyses of within study results.
5. Repeat the analyses requested in comments 3 and 4 just among patients who have a prior CV history or risk factors for CV disease. Provide analyses separated by trial and integrated across the trials in the PCSA database.

In order to facilitate the review of your submission, provide the requested information no later than the close of business Monday, February 2, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

^[1]Chuang-Stein, C and Beltangady, M (2011). Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. *Pharmaceutical Statistics*, 10:3-7.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/January 16, 2015
Cleared by: SChaudhry/January 16, 2015
 LGilbert McClain/January 16, 2015
 LJafari/January 16, 2016
Finalized by: NTon/January 16, 2016

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/s/

PHUONG N TON
01/16/2015



BLA 125526

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

GlaxoSmithKline LLC
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Thomas Lampkin, PharmD
Senior Director, Global Regulatory Affairs

Dear Dr. Lampkin:

Please refer to your Biologics License Application (BLA) dated November 4, 2014, received November 4, 2014, submitted under section 351(a) of the Public Health Service Act for mepolizumab.

We also refer to your amendments dated December 11 and 18, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is **November 4, 2015**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 17, 2015. In addition, the planned date for our internal mid-cycle review meeting is April 14, 2015.

We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

1. The concerns outlined in the End of Phase 2 (EOP2) meeting held on May 4, 2012, and Pre-BLA meeting held on January 15, 2014, regarding identifying and labeling the targeted patient population remain. The adequacy of the data, including data from negative trials, and the wording of the proposed indication statement will be review issues. These will likely be subjects for discussion at the advisory committee meeting.
2. We note that the proposed indication is for patients 12 years of age and older. The limited number of adolescents in your development program may not be sufficient to support an indication in adolescents and will be a review issue.
3. The limited representation of minority groups, specifically African-Americans and Hispanics, in your development program is a concern. The adequacy of your program to be generalizable to the population without racial limitation will be a review issue and likely a subject for discussion at the advisory committee meeting.
4. We note the lack of data supporting your recommendations for handling parasitic disease. This issue may require a post-marketing requirement (PMR).
5. The use of the SGRQ in asthma trials is without regulatory precedent and inclusion of the SGRQ data into product labeling will be a review issue.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list

each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

We note that you have submitted pediatric studies with this application for pediatric patients 12 to 18 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this age group.

If you have any questions, call Nina Ton, Regulatory Project Manager, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

LYDIA I GILBERT MCCLAIN
01/12/2015
Acting Division Director

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and your proposed analysis plan for the tipping point sensitivity analyses submitted on December 18, 2014. We have the following comments:

The proposed general approach to conduct tipping point analyses by investigating a range of fixed assumptions about patient outcomes after dropout on both arms (e.g., exacerbation rates ranging from 1 to 5 per year) is acceptable, and the proposed presentation approach is reasonable. However, we have specific comments on the two methods proposed.

1. Given the single-imputation procedure proposed under approach (a), we agree that the use of the estimated variance from the completed dataset would not be appropriate. But we do not believe that the variability estimated in the primary analysis model will accurately capture the true variability in the all-randomized population. With such an imputation-based framework, we recommend multiple imputation to more appropriately estimate the uncertainty in the treatment effect under specific assumptions about the missing data.
2. For approach (b), we agree that the proposed statistic appears to provide an appropriate estimate of the *de facto* log rate ratio, given fixed assumptions about the exacerbation rates after dropout. However, we believe that an appropriate estimate of the variance of the proposed statistic would need to account for both the variance of the estimate of $[\log(\mu_M), \log(\mu_P)]$ and the variance of $[T_M, T_P]$.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/January 12, 2015
Cleared by: GLevin/January 12, 2015
LJafari/January 12, 2015
Finalized by: NTon/January 12, 2015

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/s/

PHUONG N TON
01/12/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information:

1. Conduct exposure-response analysis to assess effects of exposure, baseline eosinophil count and other risk factors on exacerbation as binary outcomes (e.g., number of exacerbations ($n \geq 2$) (yes or no?), and $n \geq 3$ (yes or no?)) based on studies MEA112997 and MEA115588.
2. Conduct time-to-event analysis to assess effects of baseline eosinophil count, exposure and other risk factors on the time to first exacerbation based on studies MEA112997 and MEA115588.
3. Submit a brief report with necessary details. Datasets and modeling scripts should be submitted based on the requirements as specified in the link (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>).

In order to facilitate the review of your submission, provide the requested information no later than the close of business Friday, February 6, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/January 9, 2015

Cleared by: JYu/January 9, 2015
LJafari/January 9, 2015

Finalized by: NTon/January 9, 2015

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/s/

PHUONG N TON
01/09/2015

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information:

1. Clarify how the following time-periods are defined for the concomitant medication tables in your completed study reports: prior to run-in, during run-in, treatment period and post-treatment period.
2. We note instances where the number of patients who started a LABA during the treatment period exceeds the number of patients not on a LABA before run-in (see CSR MEA112997 placebo arms from Tables 5.24 and 5.26 for an example). Please clarify.
3. Provide a tabulation of the number of subjects on ICS + LABA alone, ICS + LABA + additional controller medication, and ICS + non-LABA controller medication (not on a LABA) for studies MEA 112997, MEA115575 and MEA115588. We request data for the time period before run-in, during run-in, treatment period, post-treatment.
4. Provide the line listings for the cases that were evaluated for systemic and local hypersensitivity reactions.

In order to facilitate the review of your submission, provide the requested information no later than the close of business Tuesday, January 20, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/December 30, 2014
Cleared by: LJafari/December 30, 2014
 LGilbert McClain/December 30, 2014
 SChaudhry/December 31, 2014
Finalized by: NTon/December 31, 2014

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/s/

PHUONG N TON
12/31/2014

BLA 125526
Mepolizumab
GSK

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and have the following requests for information:

1. Provide the following information regarding Study Protocol MEA112997 (Oklahoma Jeremy Cole, MD clinical site):
 - a. Subject discontinuation (if applicable per treatment group: site subject number, screening visit date, randomization date (if applicable), date of first dose/last dose, date of discontinuation, reason for discontinuation)
 - b. Randomization list
 - c. Concomitant medication list (non-study medications)
 - d. All adverse events [If applicable per treatment group: preferred term/investigator entry, date start/stopped, severity/resolution, Serious Adverse Event (yes, no), death (yes/no)]
 - e. Primary efficacy endpoint (site subject number, visit # and corresponding date (baseline, week 1...end-of-study visit or Week #, etc)
 - f. Secondary efficacy endpoints (for information on FEV1, provide raw FEV1 data for pre- and post-bronchodilator measurements over the 52-week treatment period. Also, where applicable, raw scores for the St. George's Respiratory Questionnaire).
2. In a separate file, provide similar information as listed above for Study Protocol MEA115588 (Baltimore Mark Liu, MD clinical site).

In order to facilitate the review of your submission, provide the requested information no later than the close of business Monday, January 19, 2015. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/December 9, 2014

Cleared by: LJafari/December 9, 2014
AOrencia/December 10, 2014

Finalized by: NTon/December 30, 2014

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/s/

PHUONG N TON
12/30/2014

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and we have the following requests for information:

1. Presentation of results with missing data is a review issue. We are interested in the evaluation of de facto estimands, e.g., comparisons between treatment groups with respect to the exacerbation rate over 52 weeks in all randomized patients regardless of adherence. The primary analysis assumes that data after patients withdraw from the study are missing at random, i.e., that patients who drop out would be expected to have a similar exacerbation rate post-withdrawal to the exacerbation rate of patients on that treatment arm who remain in the study (and who have similar values of those baseline characteristics included in the model). This is a strong and unverifiable assumption. Therefore, to examine the potential effect of missing data on your results, we request additional tipping point sensitivity analyses for the primary endpoints in Studies MEA112997, MEA115575, and MEA115588. These analyses should vary assumptions about average values of the primary endpoint among the subsets of patients on the mepolizumab and placebo arms who withdrew from the study early. For example, in Study MEA112997, the analysis should vary assumptions about the rates of clinically significant exacerbations after dropout in the subsets of patients on both arms who withdrew early. These varying assumptions should include the possibility that patients with missing data from the mepolizumab arms had worse outcomes (a greater exacerbation rate post-withdrawal) than dropouts on the placebo arm. The goal of the tipping point analysis is to identify assumptions about the missing data under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect. Then, the plausibility of those assumptions can be discussed.

Provide the datasets and programs for these sensitivity analyses. The analysis datasets should include a column or columns which clearly indicate whether each observation was missing, observed while the patient was on randomized treatment, or observed after the patient discontinued randomized treatment.

2. Define 'baseline stability limit' listed as the first OCS dose reduction criterion in Table 3 on page 24 of your report for Study MEA115575.
3. Provide analysis datasets and programs used to produce the analyses and four figures in Attachment 1 of the study report for Study MEA112997.

We request a response by the close of business Friday, December 19, 2014. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526
Mepolizumab
GSK

Drafted by: NTon/December 11, 2014
Cleared by: LJafari/December 11, 2014
 BAbugov/December 12, 2014
 GLEvin/December 12, 2014
Finalized by: NTon/December 12, 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
12/12/2014

Dear Dr. Lampkin:

We are currently reviewing your BLA submitted on November 4, 2014, and we have the following requests for information:

We request that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Items 1 and 2). This information is requested for trials MEA112997 and MEA115588. Please note that if the requested items are provided elsewhere in submission in the format described, you can describe location or provide a link to the requested information.

The dataset that is requested in Item 3 below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where Office of Scientific Investigations (OSI) requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

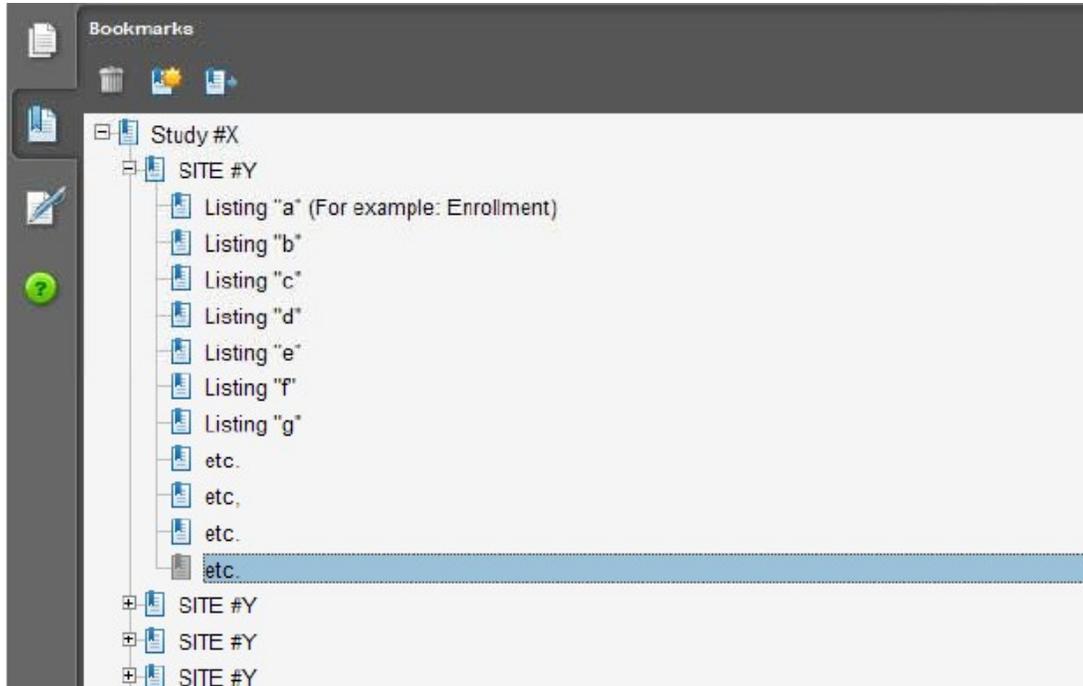
1. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

- a. Include the following information in a tabular format in the original BLA for each of the completed pivotal clinical trials (MEA112997 and MEA115588):
 - i. Site number
 - ii. Principal investigator
 - iii. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - iv. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If you are aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
- b. Include the following information in a tabular format, by site, in the original BLA for each of the completed pivotal clinical trials:
 - i. Number of subjects screened at each site
 - ii. Number of subjects randomized at each site
 - iii. Number of subjects treated who prematurely discontinued for each site by site
- c. Include the following information in a tabular format in the BLA for each of the completed pivotal clinical trials:
 - i. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection.

- ii. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - iii. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
- d. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
- e. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

2. Request for Subject Level Data Listings by Site

- a. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
- i. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - ii. Subject listing for treatment assignment (randomization)
 - iii. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - iv. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - v. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - vi. By subject listing, of AEs, SAEs, deaths and dates
 - vii. By subject listing of protocol violations and/or deviations reported in the BLA, including a description of the deviation/violation
 - viii. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - ix. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - x. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
- b. We request that one PDF file be created for each pivotal phase 2 and phase 3 study using the following format:



3. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry, *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning*, (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-BLA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Please note providing us with the requested data for trials MEA112997 and MEA115588 is voluntary; however, providing this information will assist us in selection of clinical investigational sites to audit.

If you are able to provide these data, we request a response by the close of business Friday, December 12, 2014. You may submit your response via telephone facsimile at 301-796-9728, or by email to phuong.ton@fda.hhs.gov, followed by an official submission to your BLA.

If you have any questions, please contact Nina Ton, Regulatory Project Manager, at 301-796-1648.

BLA 125526

Drafted by: SChaudhry/November 19, 2014
Cleared by: LGilbert McClain/November 19, 2014
LJafari/November 19, 2014
Finalized by: NTon/November 19, 2014

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/s/

PHUONG N TON
11/19/2014



BLA 125526

BLA ACKNOWLEDGMENT

GlaxoSmithKline LLC
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Thomas Lampkin, PharmD
Senior Director, Global Regulatory Affairs

Dear Dr. Lampkin:

We have received your Biologics License Application (BLA) submitted under section 351(a) of the Public Health Service Act (PHS Act) for the following:

Name of Biological Product: Mepolizumab 100 mg SC

Date of Application: November 4, 2014

Date of Receipt: November 4, 2014

Our Reference Number: BLA 125526

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 3, 2015, in accordance with 21 CFR 601.2(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 601.14(b) in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action. The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The BLA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy, and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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
11/14/2014



BLA 125526

INFORMATION REQUEST

GlaxoSmithKline LLC
Attention: Thomas Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. Lampkin:

Please refer to your Biologics License Application (BLA) dated November 4, 2014, received November 4, 2014, submitted under section 351(a) of the Public Health Service Act for Mepolizumab 100 mg SC.

We are reviewing your submission and have the following comments and information requests. We request a written response by October 7, 2015 in order to continue our evaluation of your application.

Information Request for BLA 125526 – Quality Micro

1. Please respond to the following comments regarding (b) (4)

(b) (4)
- c. Describe the leak integrity test performed by the supplier, indicate the test method sensitivity in terms of detectable leak size, and summarize the method validation data.

2.

(b) (4)

b. Dates for which these studies were conducted

If you have questions, call Melinda Bauerlien, Regulatory Business Process Manager at (301) 796-0906.

Sincerely,

**Melinda J.
Bauerlien -S**

Digitally signed by Melinda J. Bauerlien -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300178565,
cn=Melinda J. Bauerlien -S
Date: 2015.09.30 14:42:01 -04'00'

Melinda Bauerlien, M.S.
Senior Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research



IND 6971

MEETING MINUTES

GlaxoSmithKline
Attn: Dr. Ilse Blumentals
Director, Global Regulatory Affairs
709 Swedeland Road
King of Prussia, PA 94949

Dear Dr. Blumentals:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mepolizumab.

We also refer to the meeting between representatives of your firm and the FDA on August 5, 2014. The purpose of the meeting is to provide an update and seek feedback from the Agency on the Chemistry, Manufacturing and Controls development, manufacturing process and process validation strategy for registration.

A copy of the official minutes is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me.

Sincerely,

{See appended electronic signature page}

Marjorie Shapiro, Ph.D.
Chief, Laboratory of Molecular and Developmental Immunology
Division of Monoclonal Antibodies
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: CMC Only

Meeting Date and Time: August 5, 2014 at 9:30 A.M.
Meeting Format: Face to Face

Application Number: 6971
Product Name: mepolizumab
Sponsor/Applicant Name: Glaxo/Smith/Kline, Inc.

Meeting Chair: Marjorie Shapiro
Meeting Recorders: Andrew Shiber

FDA ATTENDEES:

Center for Drug Evaluation and Research

Office of Biotechnology Products (OBP)

Marjorie Shapiro Team Leader, Division of Monoclonal Antibodies (DMA)
Jennifer Swisher Product Quality Reviewer, DMA
Jabril Abdus-Samad Labeling Review, OBP
Andrew Shiber Regulatory Project Manager, OBP

Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Sophia Chaudhry Medical Officer, DPARP

Office of Clinical Pharmacology (OCP)

Ji Ping Pharmacology, OCP

Office of Biostatistics (OB)

Xiaoyu Dong Statistics Review, OB

SPONSOR ATTENDEES

Robert Clemmitt Senior Director, Mepolizumab Biopharmaceutical Medicine and Process Delivery Leader
Thomas Lampkin Senior Director, Global Regulatory Affairs
Ilse Blumentals Director, CMC Biopharmaceutical Regulatory Affairs
Myrna Monck Manager, Biopharmaceutical Product Sciences
Jennifer Dally Manager, Biopharmaceutical Analytical Sciences
Sagun Shakya Manager, CMC Biopharmaceutical Regulatory Affairs
Alexandra Beumer-Sassi Regulatory Executive, CMC Biopharm Regulatory Affairs
Devin Lausch Manager, Biopharmaceutical Production

1.0 BACKGROUND

Name of drug: mepolizumab

Indication: As an add-on treatment for patients with severe eosinophilic asthma.

Objectives: To provide an update and seek feedback from the Agency on the Chemistry, Manufacturing and Controls development, manufacturing process and process validation strategy for registration.

2.0 DISCUSSION

The Sponsor submitted a slide presentation before the meeting to facilitate discussion which is attached to this meeting minutes.

Question 1: Does the Agency agree on the data package and the mitigation strategies to be used in support of the use of the (b) (4) for registration?

FDA Response to Question 1:

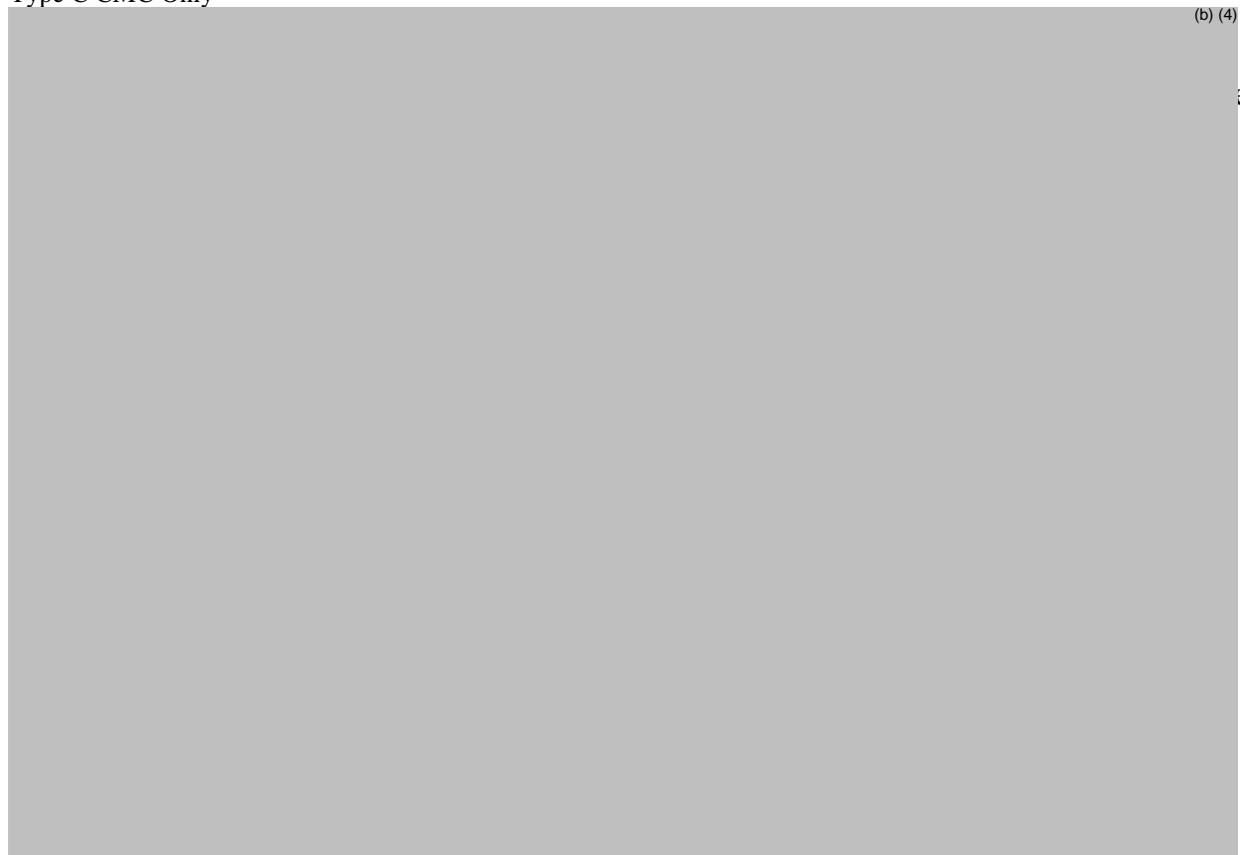
In general, your mitigation strategies are acceptable. (b) (4)

[Redacted content]

Meeting Discussion: (b) (4)

[Redacted content]

[Redacted content]



(b) (4)

e
s

The Agency stated that the decision on DS shelf-life would be a review issue.

Question 2: Does the Agency agree on the assessment of Critical Quality Attributes for mepolizumab and the proposed testing strategy for commercial manufacture? Does the Agencies have any further comments on this proposal?

FDA Response to Question 2:

In general, we agree with the assessment of Critical Quality Attributes for mepolizumab and the proposed testing strategy for commercial product, but a final determination regarding their acceptability will be a BLA review issue. We have the following comments that should be addressed in the BLA.



(b) (4)

(b) (4)

(b) (4)

- Process related impurities (b) (4) should be included in comparability studies when major manufacturing changes are introduced.

Sponsor Response:

(b) (4)

- We agree that effector function is unlikely to play a role in the mechanism of action of mepolizumab. However, we note the article by Jiang et al (Advances in the assessment and control of the effector functions of therapeutic antibodies. Nature Reviews Drug Discovery. 2011 volume 10) that recommends an evaluation of mAbs with low potential for effector function using an appropriate in vitro system to confirm a lack of effector function.

Sponsor Response:

- **There are multiple lines of evidence that demonstrate that IL-5 is a soluble antigen and that Fc functionality is not involved in MOA of mepolizumab.**

- **Sequence and structure of IL5 indicates it is a secreted protein (no membrane domains)**
- **IL-5 and Mepolizumab (b) (4) structure analysis demonstrate that mepolizumab binding prevents IL-5 from binding to the cell receptor due to steric hindrance.**
- **Safety assessment studies provide further evidence that IL-5 is not present on cell surfaces.**
- **GSK will provide details on this information in CQA section (S.2.6)**

Meeting Discussion: The Agency explained that Fc functionality is a topic for scientific discussion not regulatory discussion. In the next five years Fc receptor biology may become a regulatory discussion.

Question 3: Does the Agency agree with the proposed statistical approach to assess comparability of stability profiles?

FDA Response to Question 3:

No, FDA does not agree with your proposed (b) (4) procedure to assess whether the comparability of stability profiles between the pre-change and post-change manufacturing processes.

Sponsor Response:

Comparability of (b) (4) and MDP1/MDP2 includes:

- **Extended biophysical and biochemical comparability of DS and DP**
- **Batch Analysis**
- **Forced Degradation**
- **Stability**
- **Process Performance**
- **Impurity Clearance**
- **Viral Clearance**

The purpose of the statistical approach is to establish comparability of the stability profiles between (b) (4) and MDP1/MDP2. (b) (4) MDP1 have 60 months of stability data. GSK proposes to (b) (4) to establish a commercial shelf life of (b) (4) for (b) (4) and MDP2.

Meeting Discussion:

(b) (4)

Any additional degradation products resulting from the manufacturing change should be clearly specified in your stability study report.

Sponsor Response:

- **There are no additional degradation products resulting from the manufacturing change.**

Main differences in the stability data, including different number of batches and/or different testing frequency or period, as well as different measurement methods should be stated in the stability study.

Sponsor Response:

Statistical Analysis includes:

-
-
-
-

(b) (4)

Mepolizumab (b) (4) MDP1 stability profiles show that there is essentially no change in any of the attributes over (b) (4) at recommended storage conditions.

- **To date, results of (b) (4) MDP2 stability studies are consistent with historical performance.**

Stability profile comparison may not be meaningful if those main differences exist.

Our specified comments on your statistical approach for stability profile comparison are summarized below.

(b) (4)

Sponsor Response:

GSK acknowledges ICH Q1E guidance on significance levels for pooling stability batches.

(b) (4)

Graphical display of individual stability data will be provided in the BLA.

Meeting Discussion: The Agency asked about how the batches will be paired for statistical analysis and what is the worst case scenario slope that was selected in the case the data could not be pooled. The sponsor noted that the batches will not be paired and that the analysis was performed on the slope differences of drug substance and drug product from the two processes. If the batches can't be pooled the worst case slope is selected. The Agency told the sponsor to consider other worst case options such as selecting batches with the largest slope difference instead of the largest slope.

In addition, establishment which (b) (4) is recommended for assessing significance of batches. In addition, establish of both pooling and no degradation does not necessarily mean that stability profiles are comparable. In this case, graphic display of individual stability data can be helpful to detect differences between the two manufacturing processes. Moreover, please provide information on how many (b) (4) MDP2 batches will be included in the study.

(b) (4)

Sponsor Response:

- **Equivalence testing will only be performed in the presence of a significant slope**

Meeting Discussion: The Agency noted that the slope is zero, which means there is still variability in the data. Graphically explain the data in the BLA.

More specifically, if the 90% confidence interval of the slope difference of two batches is within a pre-specified acceptance limit, the two stability profiles are comparable.

Sponsor Response:

- **For a given attribute, the assessment is performed on the slope differences of DS / DP from the two processes, not two batches. There is no pairing of batches.**

In the case that the stability data show a linear trend, please provide how the acceptance limits will be established.

Sponsor Response:

Will provide the acceptance limit equation and explain in the BLA.

In addition, please specify how individual batches from pre-change and post- change processes will be paired for equivalence test and also consider statistical comparison on the intercepts. If the stability data show a non-linear trend, equivalence tests based on the linear slopes are inappropriate. Thus, we recommend (b) (4) are inappropriate. Thus, we recommend including a graphic individual stability data from both processes for each testing parameter.

Sponsor Response:

- **Sponsor agreed that graphic display of data will be helpful and be provided.**

Question 4: Quick Response (QR) codes may be helpful for both, Health Care Professionals and patients to access relevant information quickly and easily once a prescribing decision has been made.

A) Does the Agency agree that a QR code may be placed on an inside flap of the mepolizumab product carton to allow a direct link to a short video demonstrating proper technique for reconstitution of mepolizumab drug product?

FDA Response to Question 4a:

Note that FDA has not developed a formal position on the use of QR codes. However, placing a QR code on an inside flap appears reasonable, as this location is unlikely to compete with or distract from the bar code and any required or recommended information on the labels and labeling. QR code location and prominence as well as the reconstitution instructions for mepolizumab, will require review during the standard labeling review process after BLA submission.

Meeting Discussion: The Agency noted that the Office of Prescription Drug Promotion (OPDP) will need to review. The Agency also clarified that the QR code should not interfere with the bar code and other regulatory information required on the package.

Post Meeting Comment: The sponsor is welcome to submit their proposed websites to OPDP (not to the BLA/IND) for advisory review any time after the BLA has been filed. However, the review would depend largely on the status of the labeling and the content of the sponsor's proposed piece. Therefore, the review of these materials may be delayed until a substantially complete PI (SCPI) is available. This is particularly important because, depending on the claims made in the piece, they may need to be balanced with appropriate safety information.

It may be possible for OPDP to review a proposed piece (b) (4) prior to the SCPI being complete and include a reminder that the piece would need to be updated with any labeling changes. However, the proposed piece would need to be viewed first before that determination could be made.

B) (b) (4)
(b) (4)

FDA Response to Question 4B:

The Agency would not object to the use of a (b) (4)
(b) (4)
. We remind you that

[REDACTED] (b) (4)

[REDACTED]

Question 5: As part of the lifecycle for mepolizumab, [REDACTED] (b) (4)

[REDACTED]

FDA Response to Question 5:

We may agree to your proposed meeting request. However, our ability to have a meeting to [REDACTED] (b) (4) would depend on the timing of the request relative to internal GRMP deadlines, PDUFA milestones and inspectional activities.

Additional FDA Comments

[REDACTED] (b) (4)

Product Quality Microbiology

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Please include in the BLA submission a complete list of manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided to facilitate the planning of the pre-license inspections.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain the following product quality microbiology information:

- Evidence of monitoring of bioburden and endotoxin levels at critical manufacturing steps using qualified bioburden and endotoxin tests. Pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful product (b)(4) validation runs at manufacturing scale. Bioburden and endotoxin levels (b)(4) should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- (b)(4) (3.2.S.2.5).
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5).
- Data summaries of shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications. The bioburden limit should be (b)(4) for bulk materials allowed to be stored for extended periods of time at refrigerated temperatures (3.2.S.4).
- Qualification data for bioburden and endotoxin test methods performed for (b)(4) drug substance (3.4.S.4).

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries supporting the (b)(4) and sterility assurance.

For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:

- (b)(4)
- Sterilization (b)(4) of equipment and components that contact the sterile drug product. The equipment requalification program should be described.
- (b)(4) microbial controls and hold times. Hold times should be validated at manufacturing scale.
- (b)(4), if applicable.
- Three successful (b)(4), including summary environmental monitoring data obtained during the runs. (b)(4) and environmental monitoring procedures should be described.
- A description of the routine environmental monitoring program.
- Shipping validation studies,
- The lyophilization process, if applicable.

The following method validation information should be provided:

- Container closure integrity testing (3.2.P.2.5). System integrity (including maintenance of the (b) (4)) should be demonstrated for the complete manufacturing process. Container closure integrity methods validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress and should include routine manufacturing process defects as controls. We recommend that container closure integrity testing be performed *in lieu* of sterility testing for stability samples at the initial time point and every 12 months (annually) until expiry (3.2.P.8.2).
- Qualification data for bioburden, sterility and endotoxin test methods performed for (b) (4) (where applicable) and the drug product, as appropriate (3.2.P.5).
- Perform the Rabbit Pyrogen Test on three batches of drug product in accordance with 21 CFR 610.13(b).

- (b) (4)

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/s/

MARJORIE A SHAPIRO
09/17/2014



IND 006971

MEETING MINUTES

GlaxoSmithKline LLC
5 Crescent Drive
Philadelphia, PA 19112

Attention: Thomas Lampkin, Pharm.D.
Senior Director, Global Regulatory Affairs

Dear Dr. Lampkin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mepolizumab.

We also refer to the meeting between representatives of your firm and the FDA on January 15, 2014. The purpose of the meeting was to discuss the submission of a Biologic License Application for mepolizumab in the treatment of patients with severe eosinophilic asthma.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, Pharm.D.
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: January 15, 2014; 1:00 – 2:30 PM ET
Meeting Location: White Oak Building 22, Conference Room 1311

Application Number: IND 006971
Product Name: Mepolizumab
Indication: Asthma
Sponsor: GlaxoSmithKline

Meeting Chair: Badrul Chowdhury, M.D., Ph.D.
Meeting Recorder: Nina Ton, Pharm.D.

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Susan Limb, M.D., Clinical Team Leader, DPARP
Sofia Chaudhry, M.D., Clinical Reviewer, DPARP
Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader, DPARP
Nina Ton, Pharm.D., Regulatory Project Manager, DPARP
Joan Buenconsejo, Ph.D., Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Yongman Kim, Ph.D., Biostatistics Reviewer, Division of Biometrics II, OB
Satjit Brar, Pharm.D., Ph.D., Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Ping Ji, Ph.D., Clinical Pharmacology Reviewer, DCPII, OCP
Marjorie Shapiro, Ph.D., Chief, Laboratory of Molecular and Developmental Immunology, Division of Monoclonal Antibodies (DMA), Office of Biotechnology Products (OBP)
Tamra Meyer, Ph.D., M.P.H., Epidemiologist, Division of Epidemiology II, Office of Pharmacovigilance and Epidemiology
Dipti Kalra, R.Ph., LCDR, Safety Evaluator, Division of Pharmacovigilance I, Office of Pharmacovigilance and Epidemiology

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim, Independent Assessor

SPONSOR ATTENDEES

Steve Yancey, Vice President, Medicine Development Leader
Hector Ortega, M.D., Director, Clinical Development
Thomas Lampkin, Pharm.D., Senior Director, Regulatory Affairs

GSK Attendees by Teleconference

Oliver Keene, Director, Clinical Statistics
Isabelle Pouliquen, Director, Clinical Pharmacology
Amy Loercher, Manager, Clinical Immunology
Tim Hart, Director, Safety Assessment
Ilse Blumentals, Director, CMC Regulatory Affairs
Mauri Fitzgerald, Vice President, Regulatory Affairs
Karen Miller, Senior Director, Regulatory Affairs
Deb Templeton, Director, Global Clinical Safety and Pharmacovigilance

1. BACKGROUND

GlaxoSmithKline submitted a Pre-BLA meeting request dated October 18, 2013, to the Division of Pulmonary, Allergy, and Rheumatology Products. The purpose of the meeting was to discuss the submission of a Biologic License Application for mepolizumab, a humanized monoclonal antibody, in the treatment of patients with severe eosinophilic asthma. Upon review of the meeting package, the Division provided preliminary comments to GSK's questions via electronic correspondence on January 10, 2014. Thomas Lampkin, Senior Director, Regulatory Affairs, GSK, communicated to the Division via email dated January 13, 2014 that GSK requested to focus the meeting discussion to the Introductory Comments, Questions 6, 7, 12c, and 15b. Question 11b was also discussed during the meeting. The Sponsor's questions are in *italics*, the FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

CLINICAL/REGULATORY

Introductory Comment

The planned submission appears adequate for filing. Whether the application is adequate to support the proposed indication will be a review issue. In general, we find it difficult to provide detailed feedback on the proposed application given the limited information available from the confirmatory trials. We continue to have the same concerns with the overall development program that were identified during the May 4, 2012, End-of-Phase 2 meeting. These concerns are highlighted in the following comments.

- We are uncertain of the data to support the proposed mepolizumab 100 mg subcutaneous dose. The adequacy of the proposed bridging between the 75 mg IV and 100 mg SC will be a review issue. If the proposed bridging is deemed inadequate, then the clinical program will lack replication for the proposed 100 mg SC formulation. Furthermore, earlier data suggested that lower doses of mepolizumab may also be efficacious. Depending on the safety profile, the adequacy of dose-ranging may be in question.
- We remain unclear on the extent of long-term exposure data that will be available specifically for the 100 mg SC dose. As noted previously, any safety differences observed between the IV and SC doses will jeopardize the proposed bridging strategy. In general, the BLA should be complete at the time of submission.

Meeting Discussion

GSK discussed the long-term exposure data for the 100 mg SC dose by summarizing the information presented in Slide 1 and 2 (attached) and asked FDA for feedback. FDA inquired if the SC dose has been used in other non-asthma studies. GSK responded that studies for other indications use the IV dose; however, SC administration will be used in the (b) (4). FDA acknowledged the clarification and

confirmed with GSK that the open-label extension studies will extend after the BLA submission. FDA advised GSK to submit a complete BLA application.

- As noted during the EOP2 meeting, the clinical program will need to justify the proposed restriction of mepolizumab to a subset of asthma patients. Information from other asthma subpopulations will assist in the risk-benefit assessment and may be included in the label to assist in selecting appropriate patients for treatment. During the EOP2 discussion, you indicated that you had negative data from previously conducted studies in a wider asthmatic population to support the proposed restriction. To that end, provide the complete study reports and datasets from these studies in your BLA submission.

Meeting Discussion

GSK agreed with FDA's recommendation during the EOP2 meeting to include negative data from its published studies to help select the target patient population for treatment. GSK stated that study MEA112997 identified the target population who would benefit from the drug by inclusion of two key parameters in the program: history of exacerbation at baseline and threshold of blood eosinophils ≥ 150 cells/mcl. FDA asked if GSK has conducted other published or non-published studies including negative ones other than the studies presented in the slides. GSK responded there were two negative studies; Study 006 (b) (4) using the IV dose (b) (4)

FDA commented that the Agency would review and evaluate all data to gain an understanding of the drug effect on the whole asthma population and that all data (both positive and negative) will be included in the product label. GSK agreed to include all studies in the submission. FDA reiterated that full datasets for all studies would need to be provided in the BLA submission.

- The BLA submission and proposed labeling will need to address the potential impact of mepolizumab on underlying parasitic disease.

Meeting Discussion

GSK acknowledged that while it would be appropriate to address the impact of the drug on patients with parasitic disease, the clinical trials did not enroll patients with this condition. FDA commented that parasitic infection is a typical issue for this type of drug and that it would need to be addressed in the BLA application. FDA referred GSK to other approved product labels for examples. GSK responded that it would be open to discussing and addressing this issue by risk mitigation, management with labeling, or post marketing requirement.

Question 1

The Briefing Document contains a tabulation of all completed and ongoing clinical studies that will be included in the severe asthma BLA as per discussion with the Agency at the End of Phase 2 (EoP2) meeting with FDA held May 4, 2012 (FDA Reference ID 3135005). Does the Agency agree that the clinical studies described will form the basis for an adequate submission?

FDA Response

See Introductory Comment.

Meeting Discussion

This question was not discussed.

Question 2

Following the severe asthma EoP2 meeting (May 4, 2012), GSK understands that the safety of mepolizumab in the proposed patient population will be adequately characterized for registration based on the outlined development plan. Does the Agency have any additional comments on the adequacy of the safety database for the planned submission?

FDA Response

See Introductory Comment.

Meeting Discussion

This question was not discussed.

Question 3

Does the Agency agree that safety and efficacy data from study MEA112997, and assuming replicate support from MEA115588 supports the following indication statement:

TRADENAME is indicated as an add-on treatment (b) (4) in patients 12 years and older (b) (4) blood eosinophils ≥ 150 cells/ μ l or who have had blood eosinophils ≥ 300 cells/ μ l in the past 12 months

FDA Response

Whether the data support the proposed indication will be a review issue and will likely be a topic for discussion at an Advisory Committee meeting. See Introductory Comment.

Meeting Discussion

This question was not discussed.

Question 4

As discussed during the severe asthma EoP2 meeting (May 4, 2012), GSK plans to provide a brief summary of the study and clinical results from the primary and key secondary endpoints from study MEA115575 in the Clinical Studies section of the package insert. Does FDA agree with this approach?

FDA Response

As noted during the EOP2 meeting, inclusion of study results from MEA115575 into Section 14 will ultimately be a review issue.

Meeting Discussion

This question was not discussed.

Question 5

It is proposed that adolescent data from study MEA115588 and study MEA115575 will support a pediatric indication from 12 years of age as part of the initial submission. An initial Pediatric Study Plan (iPSP) has been submitted to reflect this position (IND 006971, Serial No. 0277; November 27, 2013). Does the Division have any comments on whether the data from studies MEA115588 and MEA115575 will support a pediatric license for patients 12-17 years of age as part of the initial submission or if there are any other comments they would like to discuss at this time?

FDA Response

Your iPSP is currently under review. Specific comments regarding your pediatric program will be provided in separate letter from the Division. Whether the adolescent data are sufficient to support approval down to 12 years will be a review issue.

Meeting Discussion

This question was not discussed.

Question 6

As discussed during the severe asthma EoP2 meeting (May 4, 2012), GSK intend to request Priority Review for this submission which will provide safety and efficacy data for the reduction of severe exacerbations for the use of mepolizumab in patients with severe asthma with eosinophilic inflammation for whom appropriate standard therapy has been maximized and no alternative therapies exist. Does the Agency agree that based on this rationale, this BLA submission will qualify for Priority Review?

FDA Response

The determination of whether the submission meets criteria for priority review designation as outlined in the draft Guidance for Industry: *Expedited Programs for Serious Conditions – Drugs and Biologics* (June 2013) will be made at the time of BLA submission. However, at this time, your proposal does not appear to qualify for a priority review designation.

Meeting Discussion

GSK commented while it understood that the priority review designation would be a review issue, the Sponsor thought mepolizumab would meet the requirements outlined in the FDA guidance for expedited program for serious conditions since there is a lack of therapy for this subgroup of severe asthma patients. FDA responded that this subgroup of patients could be treated with steroids or other available therapies. FDA added that the appropriateness of priority status was difficult to determine at this stage in the absence of results from the confirmatory trials. Nonetheless, the decision to submit a request for a priority review is at GSK's discretion.

CMC

Question 7

As reviewed by FDA in previous communications, minor modifications were made to the manufacturing process for mepolizumab during clinical development (IND 006971 SN0262, SN0234, SN0214; FDA Reference ID 3257068 Feb 6, 2012). GSK has demonstrated biochemical and biophysical comparability between drug substance from the proposed commercial manufacturing process (b) (4) and from the clinical manufacturing process (b) (4) to support introduction of the new product (MDP2) into clinical studies. The briefing document for this meeting provides a summary of the analytical comparability data available to date, as well as, an outline of the analytical comparability data, clinical safety data, pharmacodynamic data, and clinical immunogenicity data that will be available for (b) (4) MDP2 and (b) (4) MDP1 at the time of BLA submission and at the Mid-Cycle review timepoint. Provided that the additional analytical characterization data confirms comparability between (b) (4) MDP1 and (b) (4) MDP2, GSK considers that the clinical safety and activity data from the OLE studies is sufficient to support registration of mepolizumab (MDP2). Does the agency concur?

FDA Response

See Introductory Comment.

Meeting Discussion

See meeting discussion under Introductory Comment.

CLINICAL IMMUNOLOGY

Question 8

The data which will be available to characterize Immunogenicity of mepolizumab administered IV and SC at the time of BLA submission is described in the briefing document. Does the Agency agree this characterization is sufficient to support registration of mepolizumab dosed SC?

FDA Response

The proposed clinical assessment of immunogenicity appears reasonable. We also request that you submit analyses of any association between immunogenicity and efficacy and adverse event rates.

Meeting Discussion

This question was not discussed.

CLINICAL PHARMACOLOGY

Question 9

Based on available guidance (including: Revised Draft Guidance: Drug Interaction Studies UCM292362, February 18, 2012), GSK believe that the clinical pharmacology package for mepolizumab outlined in this briefing document is complete and no additional clinical

pharmacology studies are needed for registration. Comments received from FDA at prior meetings (EoP2 asthma FDA Reference ID 3135005 held May 4, 2012; [REDACTED] (b) (4)

[REDACTED] did not identify any areas where additional clinical pharmacology data was needed at this time. Does the Agency agree that no additional clinical pharmacology studies are needed to support registration of mepolizumab?

FDA Response

Yes, we agree that no additional clinical pharmacology studies are needed to support registration of mepolizumab. The adequacy of the data will be a review issue.

Meeting Discussion

This question was not discussed.

NONCLINICAL

Question 10

A comprehensive package of nonclinical studies of mepolizumab has been conducted in accordance with ICH S6(R1) Guidance and will be included in the BLA. In previous discussions with FDA (FDA Meeting Minutes, [REDACTED] (b) (4)), an agreement was reached that an assessment of carcinogenic potential of mepolizumab was not required; an updated prediction of carcinogenicity for mepolizumab will be included in the BLA submission. Does the Agency agree that no further nonclinical studies are required to support the registration of mepolizumab?

FDA Response

Yes, we agree.

Meeting Discussion

This question was not discussed.

SAFETY AND EFFICACY

Question 11a

Does the Agency agree with the proposal for the grouping and integration of studies and presentation of data for the ISE?

FDA Response

Your proposal for grouping and integration of studies and presentation of data for the ISE is reasonable. Of note, we will primarily rely on the individual study results for efficacy support.

Meeting Discussion

This question was not discussed.

Question 11b

Does the agency have any comments on the proposed missing data sensitivity analyses as described in the attached Summary Document Analysis Plan?

FDA Response

For ISE purpose, the proposed missing data sensitivity analyses are reasonable. Refer to the EOP2 meeting discussion on how to handle missing data for the individual study MEA115588.

Meeting Discussion

FDA asked GSK about the status of their two Phase 3 studies, MEA112997 and MEA115588. GSK responded that study MEA112997 is complete and that MEA115588 is still ongoing. FDA clarified that the EOP2 comment on how to handle missing data provided for the COPD program applies to this study. That is, efficacy data for patients who discontinued treatment should continue to be collected and used as the primary analysis. GSK responded that not all post-withdrawal data were collected but reassured FDA that the discontinuation rate was low (less than 5%). FDA asked GSK to flag withdrawn patients with post-withdrawal data in the datasets for ease of review.

Question 12a

Does the Agency agree with the proposal for the grouping and integration of studies for the ISS?

FDA Response

The overall plan appears reasonable. Given the differences in the underlying patient populations, the safety data from the individual trials will be reviewed as well as pooled data.

Meeting Discussion

This question was not discussed.

Question 12b

Does the Agency agree with the proposal for presentation of adverse events in the ISS?

FDA Response

See response to Question 12a.

Meeting Discussion

This question was not discussed.

Question 12c

Does the Agency agree to the list of Events of Special Interest and to the proposed analysis and reporting of these Events?

FDA Response

The proposed list of adverse events of special interest appears reasonable. In addition, we have the following recommendations:

- We recommend use of the NIAID/FAAN anaphylaxis criteria (Sampson et al; JACI 2006) to determine if any of the systemic AESI reactions represent cases of anaphylaxis.

Meeting Discussion

GSK accepted FDA’s recommendation.

- In addition to your proposed line listings, provide line listing of adverse events for patients identified as having systemic reactions.

Meeting Discussion

GSK accepted FDA’s recommendation.

- We note that your definition of opportunistic AESI excludes infectious events included in the CDC definition. We recommend inclusion of all events (plus the additional events you have identified) or provide justification for why these terms were excluded.

Meeting Discussion

GSK clarified that all terms listed on pages 283 and 284 of the briefing document will be part of the analysis. FDA responded that the plan was acceptable.

Question 13

Does the Agency agree to the list of data and to the proposed analysis and reporting for data to be provided at the Mid-Cycle (Day 120/standard or Day 90/priority) review?

FDA Response

Given the uncertainties highlighted in the Introductory Comment, we find it difficult to ascertain the robustness of the application as planned. Therefore, while your proposal for the safety update may be reasonable, we remind you that the BLA should be complete at the time of submission. See Introductory Comment.

Meeting Discussion

This question was not discussed.

Question 14

For the BLA submission, GSK proposes to provide narratives and case report forms for subjects enrolled in the severe asthma Phase 2/3 and Phase 3 studies as indicated in the table below.

Severe Asthma Phase 2/3 and Phase 3 Studies

Study	Narratives				Case Report Forms			
	Death	Non-fatal SAE	Withdrawal due to AE	Pregnancy	Death	Non-fatal SAE	Withdrawal due to AE	Pregnancy
Completed at the Time of Submission								
MEA112997	X	X	X	X	X	X	X	X

MEA115588	X	X	X	X	X	X	X	X
MEA115575	X	X	X	X	X	X	X	X
Ongoing (Interim CSR)								
MEA115661	X	X	X	X				
MEA115666	X	X	X	X				

For all clinical pharmacology studies and completed studies in other indications in the mepolizumab clinical development program, narratives for deaths and non-fatal SAEs will be provided in the CSRs.

For all ongoing studies, listings of deaths and non-fatal serious adverse events (SAEs) reported up to the data cut-off date for the BLA submission will be provided in an ISS appendix.

Does the Agency agree with this proposal?

FDA Response

Your approach appears reasonable. In addition, provide case narratives for any suspected hypersensitivity drug reactions.

Meeting Discussion

This question was not discussed.

STATISTICS/CDISC

Question 15a

GSK proposes to submit datasets for studies MEA115588, MEA115575, MEA115661 (interim data) and MEA115566 (interim data) started from 2012 onwards in Clinical Data Interchange Standards Consortium (CDISC) format. We will also provide the datasets used for the ISE and ISS in CDISC format. As previously agreed at the EoP2 meeting (May 4, 2012), the company proposes that legacy asthma and Phase 1 studies are not retrospectively converted to CDISC SDTM format and will remain unchanged in legacy format. The company proposes not to submit datasets for studies in other indications (b) (4) Does the agency agree with this proposal?

FDA Response

Yes, we agree.

Meeting Discussion

This question was not discussed.

Question 15b

GSK propose to submit a draft of the CDISC package for MEA115588 (including SDTM and ADaM datasets) in June 2014 in order to ensure acceptable transmission and usability of

datasets in this format. Does the FDA Division of Pulmonary, Allergy and Rheumatology Products agree that this would be beneficial for reviewers? If so, would the FDA Division of Pulmonary, Allergy and Rheumatology Products be able to review and provide feedback on this package by end July 2014?

FDA Response

Submission of the draft CDISC package for MEA115588 is reasonable and is likely to be beneficial to reviewers to ensure usability of the datasets. To arrange a test submission, please refer to the [Submit a Sample eCTD to the FDA](#) website for guidance on sending a test submission. The sponsor may request dataset(s) analysis for CDISC specifications compliance as part of a test submission. Please notify the Agency if you want feedback for SDTM formatted datasets submitted by sending an email to esub@fda.hhs.gov. If requested, the Agency will provide reports of the dataset(s) CDISC compliance analyses of the eCTD test submission processing to the submitter. The timing of the feedback will depend on the availability of resources.

Meeting Discussion

GSK commented that it was concerned with the timing of the feedback but the Sponsor would work with FDA to ensure feedback is received in time for the BLA submission. FDA responded that while it all depends on the available resources at the time of test submission, the two-month timeframe given by GSK appears to be sufficient for us to review and to provide feedback. FDA added that GSK should either include in the Subject Header DPARP or notify DPARP Regulatory Project Manager when submitting the draft CDISC package so we can review it as well.

Question 16

GSK proposes to include SAS programs used for the efficacy and safety analyses for studies MEA112997, MEA115588, and MEA115575. Analysis Results Metadata for all results that are derived from a model as part of the CDISC package will be included for MEA115588 and MEA115575. GSK also proposes to include SAS programs used for the efficacy and safety analyses for the ISE and ISS. In addition, GSK will describe in a reviewer's guide the system of programs and macros in general terms, and describe more specifically the programs used for the primary and secondary endpoints. Does the agency agree with this proposal?

FDA Response

Yes, we agree.

Meeting Discussion

This question was not discussed.

Question 17

Previous GSK submissions to the FDA Division of Pulmonary, Allergy and Rheumatology Products have used a maximum file size of 500MB. This has resulted in some datasets being split across multiple files. For a recent submission to another FDA division, GSK was requested not to split datasets. Therefore GSK proposes for this submission to follow this latest advice and

not to split the datasets into multiple files. This may result in some files being larger than the current recommended guideline of 1GB. Does the agency have any comments on this proposal?

FDA Response

Yes, we agree.

Meeting Discussion

This question was not discussed.

3. DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. FDA advised GSK to submit a complete BLA application and asked GSK to provide the complete study reports and full datasets from all studies in the BLA submission. GSK agreed to include all studies (both positive and negative) in the submission.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.
- In addition, we note that a chemistry pre-submission meeting is planned. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

4. PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and*

Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

5. PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements of Prescribing Information](#) website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

6. ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

7. ACTION ITEMS

There were no action items.

8. SLIDES

Slides submitted by GSK for discussion during the meeting are attached.

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

/s/

PHUONG N TON
02/05/2014



IND 6971

MEETING MINUTES

Glaxo/Smith/Kline
Attention: Dr. Ilse Blumentals
Director, CMC Regulatory Affairs
2301 Renaissance Blvd
King of Prussia, PA 19406

Dear Dr. Blumentals:

Please refer to the meeting between representatives of your firm and the FDA on November 7, 2012. The meeting was for the chemistry manufacturing and controls end of phase two for IND 6971.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301)796-4798.

Sincerely,

CDR Andrew Shiber, Pharm.D.
United States Public Health Service
Office of Biotechnology Products
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Andrew.Shiber@fda.hhs.gov

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Chemistry, Manufacturing and Control
Meeting Date and Time: November 7, 2012 1:30PM Eastern Standard
Meeting Location: Face to Face

Application Number: 6971
Product Name: mepolizumab

Sponsor/Applicant Name: Glaxo/Smith/Kline

Meeting Chair: Patrick Swann
Meeting Recorder: Andrew Shiber

FDA ATTENDEES

Office of Biotechnology Products/Division of Monoclonal Antibodies (DMA)

Patrick Swann Deputy Division Directory (DMA)
Marjorie Shapiro Team Leader (DMA)

Office of Manufacturing and Product Quality/Biotech Manufacturing Assessment Branch (BMAB)

Patricia Hughes Team Leader (BMAB)
Reyes Candau-Chacon Microbiologist (BMAB)
Bo Chi Microbiologist (BMAB)

Office of New Drugs/Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

Susan Limb Team Leader (DPARP)
Sofia Chaudhry Medical Officer (DPARP)

Andrew Shiber Office of Biotechnology Products

SPONSOR ATTENDEES

Hector Ortega Director and Principal Physician Lead
Robert Clemmitt Director, mepolizumab Biopharmaceutical Medicine and Process Delivery Leader

Charles Griffin Manager, Downstream Process Development
Myrna Monck Manager, Biopharmaceutical Product Development
Jennifer Dally Manager, Biopharmaceutical Analytical Sciences
Dawn Watson Director, Regulatory Affairs and Global Regulatory Lead
Juan Gimenez Senior Director, CMC Biopharmaceutical Regulatory Affairs
Deborah Zuber Manager, CMC Regulatory Affairs, Biopharm
Ilse Blumentals Director, CMC Regulatory Affairs, Biopharm

1. BACKGROUND

The Type B meeting was for the chemistry manufacturing and controls end of phase two for IND 6971. The Agency sent preliminary feedback to the sponsor on November 5, 2012. The discussion was focused around this correspondence.

2. DISCUSSION

The questions to be discussed in this meeting from the November 5, 2012 correspondence would be 3, 9, 10, 15 and the Agency comment on the Endotoxin recovery test.

(b) (4)

(b) (4)

(b) (4)

No additional discussion needed.

Question 2: Does the Agency consider that the proposed strategy and anticipated data package are sufficient to demonstrate drug product comparability between MDP1 and MDP2?

FDA Response: The strategy to demonstrate mepolizumab drug product comparability is acceptable. We also note that the list of extended characterization assays is “tentative”. Clarify the reason these methods are “tentative”. A determination whether MDP1 and MDP2 are comparable will be made upon review of the data.

No additional discussion needed.

Question 3: Does the Agency agree that the proposed data package is sufficient to support the introduction of (b)(4) MDP2 material, representative of the intended commercial drug product, into planned Phase 3 Open Label Extension (OLE) studies?

FDA Response: (b)(4)

We agree that the proposed data package would support the introduction of (b)(4) MDP2 into the Phase 3 Open Label Study, provided that no concerns were identified upon review of the data package.

It is unclear from your meeting package whether you intend to provide clinical trial data using (b)(4) MDP2 material. In general, we expect that pivotal dose-ranging and efficacy and safety trials are conducted with the to-be-marketed product. Whether there is adequate information to bridge between clinical data obtained with the (b)(4) MDP1 product in support of the (b)(4) MDP2 product will be a BLA review issue.

Additional discussion

Sponsor Representatives: (b)(4)

(b)(4) agree that the proposed data package would support the introduction of (b)(4) MDP1 into the Phase 3 Open Label Study, provided that no concerns were identified upon review of the data package. It is unclear from your meeting package whether you intend to provide clinical trial data using (b)(4) MDP2 material. In general, we expect that pivotal dose-ranging and efficacy and safety trials are conducted with the to-be-marketed product. Whether there is adequate information to bridge between clinical data obtained with the (b)(4) MDP1 product in support of the (b)(4) MDP2 product will be a BLA review issue”.

Sponsor Representatives: From the briefing document the sponsor revised Table 3. It was noted that only (b)(4) MDP2 will be introduced into the Open Label Extension studies. (b)(4)

Agency: The FDA received confirmation that the “to be marketed product” will be used in clinical trials.

Sponsor Representatives: The sponsor wanted clarification of the Agency comment: “It is unclear from your meeting package whether you intend to provide clinical trial data using (b)(4) MDP2 material. In general, we expect that pivotal dose-ranging and efficacy and safety are conducted with the to-be-marketed product. Whether there is adequate information to bridge between clinical data obtained with the (b)(4) MDP1 product in support of the (b)(4) MDP2 product will be a BLA review issue”. GSK explained that it plans to introduce (b)(4) MDP2 into the Phase 3 Open Label Extension (OLE) study when it becomes available in the 3rd Quarter of 2013. The main driver for the introduction is to ensure

continuity of clinical supplies. The open label study will be designed to primarily assess safety and will also capture markers of asthma control. At the time of the BLA submission in the 3rd Quarter of 2014, the sponsor will include the data from the OLE study.

The sponsor also explained that it believes that the analytical testing (biochemical and biophysical characterization) is sufficient to assess comparability between (b) (4) MDP1 and (b) (4) MDP2.

Agency: The FDA would like to see data from clinical trials with the “to be marketed product” and the proposed plan could possibly be acceptable. If past experiences with the mepolizumab comparability assessments are a good predictor for the future, we don’t anticipate a problem with the proposed comparability assessment. The Agency inquired about the amount of data from the OLE study that will be in the BLA at time of filing.

Sponsor Representatives: GSK noted that there will be up to one year of clinical data in the BLA at the time of file. The sponsor believes that there is agreement on the proposed comparability strategy and the plans for the introduction of the (b) (4) MDP2 material into the asthma Phase 3 Open Label Extension studies.

Question 4: Provided that results from manufacturing process experience and extended biophysical and biochemical analysis demonstrate comparability of the manufacturing processes and of (b) (4) (b) (4) and drug product (MDP2 with MDP1), GSK proposes that no additional non-clinical or clinical studies are required in support of commercial registration of the (b) (4) MDP2 processes. Does the Agency concur with this proposal?

FDA Response: (b) (4), please see our response to question 3. Provided we concur that (b) (4) MDP2 are comparable with (b) (4) MDP1, we agree that no additional non-clinical or clinical studies will be required in support of commercial registration of the (b) (4) MDP2 processes. However, the pharmacology/toxicology and clinical reviewers will determine if the non-clinical and clinical studies are sufficient for filing a BLA for mepolizumab.

No additional discussion needed.



No additional discussion needed.

Question 6: Does the Agency consider that the proposed strategy and anticipated data package are sufficient to support use of the new analytical methods for drug substance and drug product release and stability specifications for commercial manufacture?

FDA Response: In general, we agree with the proposed strategy and data package. The acceptability of the data to support the use of the new analytical methods for mepolizumab drug substance and drug product release and stability will be a review issue.

No additional discussion needed.

Question 7: GSK considers that the proposed specification strategy and the proposed tests for release and stability are suitable to control the quality of mepolizumab drug substance and drug product for registration and commercial supply. Does the Agency concur?

FDA Response: In general, we concur with the strategy. The proposed bioburden and endotoxin specifications for drug substance and sterility and endotoxin specifications for drug product are acceptable. Overall, the commercial specifications and tests for release and stability of mepolizumab drug substance and drug product will be a BLA review issue.

We recommend that in addition to USP <788> particulate testing, sub-visible particles < (b) (4) µm in size be characterized at release and at regular intervals in the drug product stability program including under accelerated and/or stressed condition.

a) While your product should comply with compendia limits for particles greater in size than (b) (4) micron during development, it is not necessary to establish acceptance criteria at this time for smaller subvisible particles. As part of this evaluation, you should use orthogonal techniques to characterize the types of particulates.

b) It is recommended that multiple stress conditions be used to reveal the propensity of the product to form large protein particulates. A comparison of results obtained using two or more orthogonal methods will determine whether there is a correlation between the results obtained. This will allow the use of only one method for routine release and stability testing, if required. Data from these characterization studies can be used to develop and provide support in your license application for an overall control strategy for particulate matter for the manufacturing process.

No additional discussion needed.

Question 8: Does the Agency concur that three (3) full scale Drug Substance Process Performance (PPO) runs consisting of two (2) batches manufactured using (b) (4) and one (1) batch produced by (b) (4) are sufficient to demonstrate process performance qualification for the drug substance?

FDA Response: In general we concur, however it is not clear what you mean by (b) (4) since you are switching (b) (4) that the 3 PPQ lots will (b) (4).

No additional discussion needed.

Question 9: Does the Agency concur that the plan provided for the MDP2 drug product process validation and proposed data packages are appropriate for registration?

FDA Response: In general your lyophilizer validation approach is acceptable. In addition, please provide the following information in your license application:

- An assessment of the potential differences based on varying conditions during processing relative to location in the lyophilizer
- A summary of information/data justifying proven acceptable ranges during lyophilization process steps [REDACTED] (b) (4)
- A demonstration of CQA batch uniformity with justification for sampling.

Additional discussion

Sponsor Representatives: The sponsor wanted clarification on the following feedback from the Agency: “In addition please provide a summary of information/data justifying proven acceptable ranges during lyophilization process steps [REDACTED] (b) (4)

[REDACTED] GSK presented a slide that provided the following clarification points on the lyophilization validation. The following data will be presented in the BLA:

[REDACTED] (b) (4)

Agency: Please describe the impact of scale for the lyophilization step from pilot scale to up to commercial manufacturing.

Sponsor Representatives: The representatives explained that it is evaluating lyophilization performance [REDACTED] (b) (4)

[REDACTED] to provide understanding of the impact of scale on the performance of the lyophilization step.

Agency: GSK should include in the BLA application the justification for why the [REDACTED] (b) (4) [REDACTED]. They also indicated that the BLA should include information on the understanding of the differences between the pilot and commercial scales.

Sponsor Representatives: GSK explained that it will provide information in the BLA submission to demonstrate the scalability of the lyophilization process.

Question 10: [REDACTED] (b) (4)

(b) (4)

FDA Response: The proposed performance qualification strategy and data package appears to be acceptable. The acceptability of the data package will be a BLA review issue. (b) (4)

Additional discussion

Sponsor Representatives: GSK provided clarification for the following FDA comments from the correspondence from November 5, 2012: **“Please clarify if the performance qualification runs of the lyophilizers** (b) (4)

The sponsor noted that for the mepolizumab project, the PPQ runs of the lyophilizers will use (b) (4). GSK intends to register the use of (b) (4) supported by validation studies.

Agency: The FDA noted that it is acceptable to use of a mix of placebo and product for large scale studies. The reference to the term placebo means an appropriate “surrogate” (b) (4) that would be representative of the product, such as (b) (4) (b) (4) without the active product.

Sponsor Representatives: GSK referred to the table included in the briefing document that summarizes the proposed experimental design to support the validation of a range for batch size. Some notes from the table:

(b) (4)

(b) (4)

FDA Response: In general, we concur with the proposed strategy. The acceptability of the process qualification will be a BLA review issue.

No additional discussion needed.

Question 12: Based on demonstrated control of Polysorbate 80 (PS80) levels in drug product, GSK proposes that routine testing for PS80 as part of the MDP2 release specification is not required. Does the Agency concur with this proposed strategy?

FDA Response: In principle we concur, but will need to review the data.

No additional discussion needed.

Question 13: GSK considers that the proposed mepolizumab drug substance and drug product stability programs are adequate to demonstrate shelf-life for the (b) (4) MDP2 materials in support of commercial registration. Does the Agency concur?

FDA Response: In general we concur, however we recommend that the container closure integrity test be conducted in lieu of the sterility test at the end of the stability program.

No additional discussion needed.

Question 14a: (b) (4)

(b) (4)

FDA Response: (b) (4)

(b) (4) Determination of the expiration dating period for mepolizumab drug substance will be a BLA review issue.

Question 14b: (b) (4)

(b) (4)

FDA Response: (b) (4)

(b) (4) . Determination of the expiration dating period for mepolizumab drug substance will be a BLA review issue.

No additional discussion needed.

Question 15: (b) (4)

(b) (4)

FDA Response: (b) (4)

(b) (4) Determination of the expiration dating period for mepolizumab drug product will be a BLA review issue.

You state on page 84 that (b) (4)

(b) (4)

(b) (4)
.” Please note that the appropriate statistical test would establish equivalence of slopes instead of testing for significant differences.

Additional discussion

Sponsor Representatives: GSK explained that there was a typographical error in the briefing document and that the proposed statistical approach is ANCOVA (analysis of co-variance rather than ANOVA). GSK also provided the rationale for the statistical analysis by stating that the use of the mixed model ANCOVA is based on the stability characteristics of mepolizumab. In the mixed model, (b) (4). Since mepolizumab has been shown to be a stable molecule, most of the data conforms to this first assessment. If results show that the slope is not zero, then all data, from legacy batches and new batches will be evaluated for comparability of slopes and intercepts.

Agency: This explanation is helpful, it is the second sentence where there is a problem; (b) (4)
Instead, the appropriate statistical test should be to establish the equivalence of the slopes. To establish equivalence you need to identify equivalence acceptance criteria and determine the confidence interval for the difference in the slope.

Sponsor Representatives: GSK noted that the appropriate members were not present to discuss the statistical approach in more depth.

Agency: Further discussion on the statistical approach used for analysis of stability trends should be included in the pre-BLA meeting.

FDA Additional Comment: Provide evidence in the BLA that the endotoxin recovery is not affected by the presence of Polysorbate and phosphate in the formulation during hold periods. Consider conducting small-scale studies to determine the effect of holding (up to seven days) on Endotoxin recovery by spiking undiluted formulated bulk with known amounts of endotoxin. These studies should be conducted in the containers of similar composition as those used for holding formulated product and samples prior to endotoxin testing.

Additional discussion

Sponsor Representatives: The sponsor explained that it currently performs spike recovery tests with endotoxin in the (b) (4). However, this is only done in a one day study in accordance to USP <85>. GSK requested clarification for the need of a 7 day study.

Agency: Although endotoxin assay interferences have been described in the literature for decades, it is a somewhat new consideration for Biopharm products. PS80 and other excipients

such as phosphates could be masking the endotoxin levels, especially when the product intermediate and/or samples are held for some time, leading to false negative data. Recently, the FDA became aware of this issue through experiences with other sponsor formulations, especially those containing PS80 and phosphates. This may be an issue depending on how the product is handled and the duration of hold times. It is important that the sponsor understands if this is a problem for the product under consideration by conducting the appropriate experiments.

The studies must be performed with the same type of container used for manufacturing because the composition of the containers may contribute to endotoxin masking. Studies should be conducted with product in the (b) (4)

Sponsor Representatives: (b) (4)

Agency: The main concern is the product container but it is possible to have the problem occur in the sample containers in addition.

Sponsor Representatives: The sponsor indicated that it will conduct the experiments to understand if this could be an issue for mepolizumab manufacturing.

Agency: Describe the strategy for testing (b) (4) subvisible particulates and suggested that this topic be included for discussion at the pre-BLA meeting.

Sponsor Representatives: GSK has been using the HIAC liquid particle counter and micro-flow imaging (MFI) technologies to monitor these particulates for the MDP1 process and will continue to do so for the MDP2 process across engineering, clinical and PPQ batches for the purpose of process characterization. The sponsor has characterized each method to understand the sources of analytical variation contributing to the reported results for mepolizumab. The sponsor agreed to include this topic in the pre-BLA meeting.

Question 16: GSK proposes to submit a drug substance and drug product stability update based on the ongoing registration batch stability protocol. The BLA amendment to provide a simple update to the stability data is projected to be between four (4) to six (6) months after the original file date. Can this update be considered within the scope of PDUFA V if there is a Solicited agreement between GSK and FDA at this EOP2 meeting?

FDA Response: Under PDUFA V, BLAs must be complete at the time of submission. However, data may be submitted to the BLA in response to an information request.

No additional discussion needed.

Additional FDA Comments

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

The CMC Drug Substance section of the BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control. The provided information should include, but not be limited to the following:

- Monitoring of bioburden and endotoxin levels (b) (4)
The pre-determined bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Three successful consecutive product (b) (4) validation runs at manufacturing scale
- (b) (4) (3.2.S.2.5)
- Bioburden and endotoxin data obtained during manufacture of the three conformance lots (3.2.S.2.5)
- Data summaries of shipping studies (3.2.S.2.5)
- Drug substance bioburden and endotoxin release specifications. (3.2.S.4)
- Provide evidence in the BLA that the endotoxin recovery is not affected by the presence of polysorbate and phosphate in the formulation (b) (4). Consider conducting small-scale studies to determine (b) (4) endotoxin recovery by spiking undiluted formulated bulk with known amount of endotoxin. These studies should be conducted in the containers where samples are held prior to endotoxin testing.

The CMC Drug Product section of the BLA (Section 3.2.P) should contain validation data summaries to support the (b) (4) operations. For guidance on the type of data and information that should be submitted, refer to the 1994 “FDA Guidance for Industry, Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”. Test methods and validation data summaries for the container closure integrity test should be submitted in Section 3.2.P.2.5 of the submission. The test method should be sensitive enough to detect breaches that could allow microbial ingress. The worst-case parameters for (b) (4) should be validated using a validated container closure integrity test.

Provide the study protocols and validation data summaries in Section 3.2.P.3.5 for the following:

- Bacterial retention study for the (b) (4)
- Sterilization (b) (4) of sterile product-contact equipment and components, and equipment requalification program
- (b) (4) microbial controls (b) (4) should be established and (b) (4) validated at manufacturing scale
- (b) (4)
- Three successful consecutive (b) (4), including summary environmental monitoring data obtained during the runs. (b) (4) simulation should cover all sterile operations
- A description of the routine environmental monitoring program
- Shipping validation of the drug product vials
- The lyophilization process

- Qualification data for bioburden, sterility and endotoxin test methods performed for (b) (4) the drug product, as appropriate (3.2.P.5)

We recommend that the container closure integrity test be performed in lieu of the sterility test for stability samples at initial time and every 12 months (annually) until expiry.

No additional discussion needed.

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/s/

ANDREW J SHIBER
02/08/2013



IND 6971

MEETING MINUTES

GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Dawn Watson
Director, Global Regulatory Affairs

Dear Ms. Watson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for mepolizumab.

We also refer to the meeting between representatives of your firm and the FDA on May 04, 2012. The purpose of the meeting was to discuss the mepolizumab Phase 2b/3 clinical results and GlaxoSmithKline's (GSK) further plans for Phase 3 studies of mepolizumab for the treatment of patients with severe ^{(b) (4)} asthma.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3367.

Sincerely,

{See appended electronic signature page}

Leila P. Hann
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: May 04, 2012, 2:00 PM
Meeting Location: FDA White Oak Campus

Application Number: IND 6971
Product Name: mepolizumab
Indication: severe (b) (4) asthma
Sponsor/Applicant Name: GlaxoSmithKline

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Leila P. Hann

FDA ATTENDEES

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sofia Chaudhry, M.D., Clinical Reviewer, DPARP
Susan Limb, M.D., Clinical Team Leader, DPARP
Feng Zhou, M.S., Statistical Reviewer, Division of Biometrics II (DBII)
Joan Buenconsejo, Ph.D., Statistical Team Leader, DBII
Liang Zhao, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCPII)
Suresh Doddapaneni, Ph.D., Deputy Director, DCPII
Robert Temple, M.D., Deputy Center Director for Clinical Science
Leila P. Hann, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Dawn Watson, Director, Regulatory Affairs and Global Regulatory Lead
Kenneth Surowitz, Vice President, Regulatory Affairs, Biopharm
Ilse Blumentals, Director, CMC Regulatory Affairs
Steve Yancey, Vice President and Medicines Development Leader
Hector Ortega, Director, and Principal Physician Lead
Dan Sikkema, Director, Clinical Immunology
Isabelle Pouliquen, Director, Clinical Pharmacology
Oliver Keene, Director, Biostatistics and Programming

1.0 BACKGROUND

GlaxoSmithKline requested a Type B End-of-Phase 2 meeting in correspondence dated December 6, 2011. The stated purpose of this meeting was to discuss Phase 2b/3 clinical results and GSK's further plans for Phase 3 studies of mepolizumab to treat severe (b) (4) asthma. Upon review of the meeting package, the Division provided responses to GSK's questions via electronic correspondence on May 1, 2012. Sponsor's questions are in ***bold italics***, Division responses are in **bold**, and meeting discussion is in normal font. Dawn Watson, Director of Global Regulatory Affairs, GSK, sent an email on May 1, 2012 to notify the Division that GSK would like to discuss Introductory Comment bullets specifically with relevance to target patient population (Question 14a), oral steroid sparing studies (Questions 6-8), labeled indication statement, when to discontinue treatment, and Questions 4 and 16a.

2. DISCUSSION

2.1. Clinical

Introductory Comment: We have the following concerns regarding the proposed development program for mepolizumab:

- **While an exacerbation indication is acceptable in principle,** (b) (4)
(b) (4)
we recommend (b) (4) **the**
exacerbation indication.

Discussion: (b) (4)
(b) (4). Noting that 30% of severe asthma patients are on chronic steroid use, the Sponsor inquired if it could include steroid-sparing data in the clinical trial section of the label. FDA stated that while such information may provide secondary support for efficacy, inclusion of this information in the label will be a review issue.

- **The labeled indication is expected to reflect the patient population studied. We note that the patient population described in the proposed indication does not directly correspond to the patients to be studied in the pivotal trials. The patient selection criteria for the efficacy trials include markers of eosinophilic inflammation. At least one of these markers, sputum eosinophilia, is a parameter which is not easily assessed in most clinical practice settings. The clinical program will need to define a patient population that can be clearly described in the product label and that clinicians can readily identify in the real world. Parameters based on more widely available assessments, such as blood eosinophilia, are more suitable for labeling and clinical practice. If you elect to target patients with severe, persistent asthma who are very poorly controlled, we refer you to the asthma control criteria outlined in**

the 2007 NHLBI/NAEPP Guidelines for the Diagnosis and Management of Asthma (EPR-3).

Discussion: Sponsor acknowledged that the criteria defining eosinophilic inflammation in the dose ranging trial was a complicated assessment. It stated its intention to simplify the entry criteria for the Phase 3 trials by focusing on the serum eosinophil measurements. GSK stated that additional post-hoc analyses from the dose-ranging trial, MEA112997, supported using serum eosinophils to define the patient population. In addition, this measurement is readily available in the clinical realm.

FDA inquired as to which population in the meeting package was the target population: eosinophilic asthma or severe (b) (4) asthma. Sponsor clarified that the target population is the subset of patients with eosinophilic asthma with more severe disease. FDA inquired as to the size of the subpopulation with this phenotype. The Sponsor estimated that 60% to 70% of the general asthma population is thought to have eosinophilic inflammation while approximately 3% of asthma patients satisfy the criteria of severe (b) (4) asthma.

FDA inquired if GSK will be using a one time serum eosinophil measurement or repeat measurements to define the population. The Sponsor stated that a baseline measurement will be used and historical levels (within the last 12 months) will also be considered. FDA stated that it may be difficult to define a phenotype based on a single measurement and that repeat measurements may be more reliable.

FDA cautioned that serum eosinophils may be impacted by other factors such as parasitic infections, particularly in multinational trials. The Sponsor clarified that the trial will exclude subjects with other causes of elevated blood eosinophil levels. The FDA noted that the selection criteria may be included in the label. Therefore, the practicality of applying this in the clinical setting should be kept in mind.

- **The clinical program will need to justify the proposed restriction of mepolizumab to a subset of asthma patients. Information from other asthma subpopulations will assist in the risk-benefit assessment and may be included in the label to assist clinicians in selecting appropriate patients for treatment.**

Discussion: Sponsor stated that based on negative data from previously published studies in a wider asthmatic population, it will focus on more severe eosinophilic disease. FDA stated that negative data may be included in the label to assist clinicians in appropriate patient selection.

- **The clinical program will need to address the appropriate duration of therapy, i.e., when to discontinue treatment if a reduction in exacerbations has been achieved.**

Discussion: Sponsor cited data that show patients return to baseline after discontinuing mepolizumab. GSK noted that there were preliminary data to support the use of serial serum eosinophil measurements to assess the need for ongoing or resumed therapy. FDA recommended that robust data be submitted as serum eosinophilia and asthma control are not currently tightly linked.

1. Target Patient Population:

Does the Agency agree that GSK has defined an appropriate target population for reducing the frequency of exacerbations following treatment with mepolizumab?

FDA Response: While the criteria based on the ATS Workshop are generally reasonable, we have concerns regarding the more specific criteria for eosinophilic inflammation. See the Introductory Comment.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

2. Exacerbation Endpoint:

Does the Agency agree that GSK has adequately characterized the exacerbation endpoint in mepolizumab studies to support an exacerbation reduction indication?

FDA Response: The exacerbation endpoint appears generally reasonable. Clarify whether the specific parameters described for the e-diary alert system, e.g., a 30% decrease in PEF on 2 or 3 consecutive days, will be used as the basis for the exacerbation definition.

Discussion: Sponsor clarified that an in-stream quality control analysis ran concurrently during the trial to verify the determination of an asthma exacerbation by the investigators. This analysis relied on standard measures of asthma deterioration such as decreased PEF or increased SABA use. If a discrepancy was noted, clinicians were asked to justify why systemic corticosteroids were prescribed or why an event was classified as such. FDA stated that this approach was reasonable and reiterated that there is no concern regarding the sponsor's definition of asthma exacerbation at this time.

3. Adolescents in Phase 3:

Does the Agency agree that this targeted number for adolescent patient exposure will be acceptable to support registration and approval of mepolizumab in patients with severe asthma 12 – 17 years of age?

FDA Response: While the proposed number appears reasonable, the adequacy of your adolescent population will depend on the nature of the efficacy and safety data and will be a review issue.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

4. Proposed Dose and Route of Administration for Remaining Phase 3 Program and Commercialization:

a. Does the Agency agree that 75mg IV and 100 mg SC are the appropriate doses to take into further Phase 3 studies?

FDA Response: We are unable to agree at this time. While the 75 mg IV dose appears reasonable for further study, the overall dose selection for Phase 3 is risky from several perspectives:

- **Based on the results of MEA112997, we note that lower doses of mepolizumab may also be efficacious. Should a safety signal be identified in the clinical program, the adequacy of the dose-ranging will be a review issue.**
- **We generally recommend that pivotal dose-ranging be conducted with the to-be-marketed formulation. There are no efficacy data to support selection of the 100 mg SC dose. The clinical relevance of serum eosinophilia, the pharmacodynamic parameter used to relate the 100 mg SC dose to the 75 mg IV dose, is unknown.**
- **Likewise, we expect replicate trials of efficacy with the to-be-marketed product. The proposed bridging between the 75 mg IV and 100 mg SC dose may be adequate to support the SC dose; however, any differences in efficacy or safety that are observed in MEA115588 between the two formulations will jeopardize this approach. If the proposed bridging strategy fails, then the clinical program will lack replication for the to-be-marketed formulation.**

Discussion: Discussion occurred under Question 4b.

- b. Does the Agency agree that no further dose ranging with the SC route of administration is required considering SC doses showed comparable pharmacodynamics and safety profiles in studies MEA112997 and MEA114092?*

FDA Response: See the response to Question 4a.

Discussion:

(b) (4)

Given the difficulty of defining the expectation more precisely, the proposed bridging approach was risky. FDA noted that other approaches may be acceptable, but the lack of clinical dose ranging data for the SC dose would need to be considered. (b) (4)

- 5. Proposed Clinical Study Designs, MEA115588 “Replication” of MEA112997:**
- a. Does the Agency agree that these changes are acceptable and that together the data generated in MEA112997 and MEA115588 will be viewed as replicate adequate and well-controlled studies (i.e., studies of similar design but different treatment durations) in the same intended target population?*

FDA Response: The change in treatment duration is at your discretion. Should MEA115588 demonstrate a clinically meaningful reduction in exacerbations, MEA112997 and MEA115588 may be viewed as replicate trials in principle, although the concern regarding the target patient population outlined in the Introductory Comment remains.

The adequacy of the data to support the proposed indication and the bridging between the IV and SC formulations will be review issues. See the response to Question 4a.

Discussion: Discussion occurred at Question 4b.

b. Does the Agency agree [redacted] (b) (4)
[redacted] ?

FDA Response: No, we do not agree. [redacted] (b) (4)
[redacted] **See the response to Question 4b.**

Discussion: Discussion occurred at Question 4b.

6. *MEA115575* [redacted] (b) (4) **Oral Steroid Sparing Studies:**
a. Does the Agency agree that the proposed patient population in studies
MEA115575 [redacted] (b) (4) *is appropriate?*

FDA Response: See the Introductory Comment.

Discussion: Discussion occurred under the Introductory Comment.

b. [redacted] (b) (4)

FDA Response: No, we do not agree. See the Introductory Comment

Discussion: Discussion occurred under the Introductory Comment.

c. [redacted] (b) (4)

FDA Response: No, we do not agree. See the Introductory Comment.

Discussion: Discussion occurred under the Introductory Comment.

7. [redacted] (b) (4)

FDA Response: See the Introductory Comment.

Discussion: Discussion occurred under the Introductory Comment.

b. [REDACTED] (b) (4)

FDA Response: See the Introductory Comment.

Discussion: Discussion occurred under the Introductory Comment.

c. *Does the Agency agree with the proposed primary efficacy endpoint?*

FDA Response: See the Introductory Comment.

Discussion: Discussion occurred under the Introductory Comment.

d. [REDACTED] (b) (4)

FDA Response: See the Introductory Comment.

Discussion: Discussion occurred under the Introductory Comment.

8. [REDACTED] (b) (4)

FDA Response: See the Introductory Comment.

Discussion: Discussion occurred under the Introductory Comment.

9. *Open-Label extension (OLE) Studies and Contribution to Safety:*

a. *Does the Agency agree that the proposed safety assessments in MEA11558, MEA115575 [REDACTED] (b) (4) and the long term data from OLEs (MEA115666 and MEA116661) be adequate to define the safety profile of SC dosing and support BLA approval?*

FDA Response: Your proposed safety assessments appear reasonable.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

10. *Labeling:*

Does the Agency agree that the clinical development program, as outlined in Section 3, will provide acceptable data to support the proposed indication (below)?

[REDACTED] (b) (4)

FDA Response: No, we do not agree. See the Introductory Comment.

Discussion: Discussion occurred under the Introductory Comment.

11. Overall Extent of Population Exposure to Assess Clinical Safety:

- a. Does the Agency agree that the extent of the proposed safety database, as listed in Table 7, be sufficient to support the initial marketing application for mepolizumab in patients with severe (b) (4) asthma?***

FDA Response: The projected size of the proposed safety database appears reasonable, but its adequacy will depend on the safety profile observed for mepolizumab.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

- b. Does the Agency agree that the plans to mitigate risk in phase, as outlined in Section 4.3, are adequate?***

FDA Response: While the outlined Phase 3 safety monitoring appears generally reasonable, we note the reporting of "infusion reaction" from the Phase 2 trials. This term is vague and may mask other adverse events, such as anaphylaxis. We recommend that you describe adverse events occurring in relation to treatment administration in as much detail as possible to facilitate the safety review. We request that you submit reports including specific signs and symptoms as well as timing. We concur with use of the diagnostic criteria for anaphylaxis as outlined by the 2006 Joint NIAID/FAAN Second Symposium on Anaphylaxis (Sampson, 2006).

Discussion: The sponsor accepted FDA's response, no discussion occurred.

2.2. Unanswered Questions from Previous Submissions

12. Neutralizing Antibody Isotype:

- a. Is the approach acceptable? If not, please provide clarification on what further information if any will be required to support BLA submission?***

FDA Response: We concur with your plan to not determine the isotype of neutralizing antibodies unless there is a correlation with clinically relevant findings.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

13. Hepatocyte Induction Study (CYP3A4):

- a. Does the Agency concur with GSK's assessment that no further evaluation is needed prior to BLA submission?***

FDA Response: Agency is unable to concur at this time that no further evaluation is needed prior to BLA submission. This is an evolving area and we suggest that you follow

developments in this area and make an appropriate decision regarding further DDI assessment. We suggest that you refer to the revised draft drug-drug interaction guidance published on February 18, 2012 for current thinking at this time; <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

14. Fast Track Designation:

a. Does the Agency concur that [REDACTED] (b) (4)

FDA Response: No, we do not agree. [REDACTED] (b) (4)

Discussion: The Sponsor asked if priority review would be possible. FDA stated that [REDACTED] (b) (4) may meet the requirements of a priority review but reiterated its concern that patient treatment will need to be optimized to ensure that patients truly have [REDACTED] (b) (4) disease.

b. Does the Agency concur with the rationale and justification provided for the [REDACTED] (b) (4)

FDA Response: No, we do not agree. See the response to Question 14a.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

c. Does the Agency agree that the proposed studies are intended to address a clinically significant aspect of asthma (i.e., exacerbation and hospitalization)?

FDA Response: Yes, we agree.

Discussion: The sponsor accepted FDA's response, no discussion occurred.

15. Potential for Accelerated Approval:

a. Does the Agency agree that the proposed study/ies are adequate to support [REDACTED] (b) (4)

FDA Response: No, we do not agree. [REDACTED] (b) (4)

Discussion: The sponsor accepted FDA's response, no discussion occurred.

16. BLA Registration:

- a. Does the Agency support the approach of an early BLA submission feasible for registration and regulatory approval?*

FDA Response: The BLA should include all efficacy and safety information that you deem necessary to support the application. While we have concerns regarding the clinical program as outlined in the Introductory Comment and preceding responses, the timing of filing is at your discretion.

Discussion: [REDACTED] (b) (4)

FDA stated that the timing of submission was at GSK's discretion. Based on the available information, the proposed application based [REDACTED] (b) (4)

[REDACTED] . FDA acknowledged that the dose-ranging trial was a large trial with positive evidence of efficacy. However, the acceptability of using this data and any post hoc analyses will be a review issue. The results need to be confirmed utilizing the target patient population.

17. CDISC:

- Does the agency have any comments on this proposal?*

FDA Response:

Your proposal to retrospectively convert study MEA112997 in a CDISC SDTM format and to not retrospectively convert any of the other completed studies is reasonable. Clarify which datasets (legacy datasets or SDTM datasets) you used to create the analysis datasets.

In addition,

- Provide all raw datasets (in SDTM format or in other format), as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report. In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.

Discussion: The Sponsor stated that their data is in legacy format and inquired if they would need to retrospectively convert that data to SDTM format. FDA clarified that legacy format is acceptable and that they would not need to perform any retrospective conversions.

- Include the programs used for creating main efficacy analysis datasets from submitted raw datasets (in SDTM format or in other format) and the programs

used for the efficacy and main safety analyses. In addition, provide a document that explains what each program is used for.

- **Provide the analysis datasets and programs used to generate the specific analyses results contained in the ISE reports.**
- **Provide the analysis datasets and programs used to generate the inferential analyses results in the ISS.**
- **You can check the FDA website to find the information about current document and guidance.**
- **Link to Study Data Specifications**
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for Industry Assessment of Abuse Potential of Drugs", available at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues were identified that require further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts were used during the meeting.

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/s/

LEILA P HANN
05/23/2012

LATE-CYCLE COMMUNICATION
DOCUMENTS



BLA 125526

LATE-CYCLE MEETING MINUTES

GlaxoSmithKline LLC
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Thomas Lampkin, PharmD
Senior Director, Global Regulatory Affairs

Dear Dr. Lampkin:

Please refer to your Biologic License Application (BLA) submitted under section 351 of the Public Health Service Act for Nucala (mepolizumab) 100 mg SC.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on August 6, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Nina Ton, Senior Regulatory Project Manager at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Lydia Gilbert-McClain, MD
Deputy Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: August 6, 2015; 12:00 – 1:00 PM EST
Meeting Location: Teleconference

Application Number: BLA 125526
Product Name: Nucala (mepolizumab)
Applicant Name: GlaxoSmithKline

Meeting Chair: Lydia Gilbert-McClain, MD
Meeting Recorder: Nina Ton, PharmD

FDA ATTENDEES

Mary Parks, MD, Deputy Director, Office of Drug Evaluation II (ODEII)
Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Lydia Gilbert-McClain, MD, Deputy Director, DPARP
Timothy Robison, PhD, Pharmacology/Toxicology Supervisor, DPARP
Marcie Wood, PhD, Pharmacology/Toxicology Supervisor, DPARP
Ruthanna Davi, PhD, Deputy Director, Division of Biometrics II, Office of Biostatistics (OB)
David Petullo, MS, Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Marjorie Shapiro, PhD, Chief, Division of Biotechnology Review and Research I (DBRRI), Office of Biotechnology Products (OBP), Office of Pharmaceutical Quality (OPQ)
Jennifer Swisher, PhD, Product Reviewer, Division of Biotechnology Review and Research IV (DBRRIV), OBP, OPQ
Jessy Kumar, PharmD, RPh, Risk Management Analyst, Division of Risk Management, Surveillance and Epidemiology (OSE)
Nina Ton, PharmD, Regulatory Project Manager, DPARP

EASTERN RESEARCH GROUP ATTENDEES

Christopher A. Sese, Independent Assessor

APPLICANT ATTENDEES

Steve Yancey, Vice President and Medicines Development Leader
Eric Bradford, M.D., Director, and Principal Physician Lead
Robert Leadbetter, M.D., Medical Director SERM, Global Clinical Safety and Pharmacovigilance
Deborah Templeton, Director SERM, Global Clinical Safety and Pharmacovigilance
Oliver Keene, Director, Clinical Statistics and Programming
Bhabita Mayer, Manager, Clinical Statistics and Programming
Isabelle Pouliquen, Director, Clinical Pharmacology

Tim Hart, Director, Pre-Clinical Safety Assessment
Linda Nelsen, Director, Patient Reported Outcomes
Robert Clemmitt, BioMPD Leader, Biopharm CMC
Michael Byrne, Director, Analytical Method Development
Alan Gardner, Director, Biopharm CMC Regulatory Affairs
Stuart Hobbs, Senior Director, Labeling, Global Regulatory Affairs
Diana Daly, Vice President, Global Regulatory Affairs
Karen Miller, Senior Director and Global Lead, Global Regulatory Affairs
Tom Lampkin, Senior Director, Global Regulatory Affairs

1. BACKGROUND

BLA 125526 was submitted on November 4, 2014, for Nucala (mepolizumab).

Proposed indication: Asthma

PDUFA goal date: November 4, 2015

FDA issued a Background Package in preparation for this meeting on July 29, 2015.

2. DISCUSSION

1. Introductory Comments

- Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues

- No substantive review issues for discussion

3. Discussion of Minor Review Issues

- We reviewed your submission dated July 27, 2015 regarding your investigation into the elevated results in the IL5 Neutralization Assay for MDP2 lots. Overall, we accept the conclusions of your investigation, but would like to discuss two items.
 1. Provide your rationale for including the (b) (4) control limit of an ED50 ratio \leq (b) (4).
 2. When the Annual Report is filed, in addition to providing updated stability data, provide a summary of the release results for all drug substance and drug product lots manufactured during the reporting period.

Discussion

GSK submitted the responses (attached) to the minor review issues on August 4, 2015. FDA found these responses acceptable. FDA added that GSK's response to the 483 is under review in the Office of Compliance (OC). FDA also noted that OC is aware of the goal date and has given it a priority review status.

4. Additional Applicant Data

- No new applicant data for discussion

5. Information Requests

- No pending Information requests

6. Postmarketing Requirements/Postmarketing Commitments

- Pregnancy Registry – PMR
- PREA – PMR – pediatric study in children 6 to 11 years ongoing; PK/PD study as part of Agency's agreed upon iPSP

Discussion

FDA found GSK's proposed Pregnancy Registry acceptable. However, FDA stated that instead of a voluntary program, it will be a PMR and as such, the protocol will need to be submitted and reviewed by our Pediatric and Maternal Health staff. FDA noted that an information request will be forth coming regarding this PMR. GSK commented that this program is handled by a third party but they will coordinate with FDA and this external group to streamline the timing.

The agreed upon iPSP has a waiver for pediatric patients less than 6 years old and a deferral for patients 7 to 11 years old. Patients 12 years and older were included in the adult asthma program. FDA informed GSK that this iPSP was discussed at the Pediatric Review Committee (PeRC) meeting this week and there was a question

(b) (4)

7. Major labeling issues

- Labeling comments sent June 24, 2015 and July 2, 2015; updated labeling received July 21, 2015

Discussion

FDA noted that there will be additional labeling comments forthcoming and highlighted several conceptual changes including: 1) removal of qualifiers (b) (4) “severe” in defining asthma; 2) revisions to the demographic table to make it less granular (GSK was referred to the Breo label demographic table for reference); and 3) changes to the (b) (4) subsection in section 14. FDA commented that the (b) (4) will be replaced with a figure displaying the (b) (4). GSK asked if the adolescent population will be part of the indication. FDA responded that although the draft indication statement that we sent to you did not include age, the efficacy and safety profile for patients 12 to 17 years old is still under review. There are ongoing discussions within the Agency regarding the inclusion of the age limit in the indication statement however, the Division’s practice for asthma labels has always been to include the age in the indication statement and ultimately, the age limit may appear in the indication statement. GSK asked whether treatment modification by blood eosinophil is determined qualitatively or quantitatively. FDA responded that this issue is also under review but it will likely be quantitatively. FDA stated that labeling should describe that the data showed that patients with higher eosinophils counts at initiation of treatment show greater benefit from mepolizumab. (b) (4)

8. Review Plans

- Reviews ongoing and on target with PDUFA goals

9. Wrap-up and Action Items

Discussion

FDA will issue an information request regarding the milestones and timeline of the PREA PMR and the Pregnancy Registry. GSK will provide a follow-up regarding the plan for the long-term safety exposure in pediatrics 6 to 11 years old, and the follow-up information regarding patients under 12 years of age (number of patients, extent of exposure, dose) in the EoE study. GSK asked FDA about the action date for this application. FDA responded that pending CMC inspection issues, the action date will be close to the PDUFA goal date.

Post-Meeting Comment

The Division had further discussion following the LCM to revisit the recommendation from the Division of Pediatric and Maternal Health (DPMH) regarding making GSK’s

voluntary pregnancy registry a post-marketing study. Upon further consideration, we have decided that a post-marketing study is not necessary and that GSK's proposal of a voluntary pregnancy registry as outlined in their submission is adequate to follow asthma patients for pregnancy outcomes. Therefore, the Division retracts the statements made at the LCM regarding a PMR for the pregnancy registry as we will not be proposing a PMR for the voluntary registry. The Agency acknowledges that the conduct of the pregnancy registry is a good public health endeavor and encourages GSK to exercise due diligence in conducting the registry.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

QUESTION 1

Provide your rationale for including the \leq (b) (4) control limit of an ED50 ratio \leq (b) (4)

Response

A (b) (4) control limit of \leq (b) (4) was introduced as an additional interim control for the IL5 neutralization bioassay at the BioCTL. The purpose of this control limit is to ensure that ED50 ratio values of (b) (4) produced at the BioCTL are investigated as these values could potentially equate to OOS values (acceptance criterion \geq (b) (4)), taking into account the observed offset of ED50 ratio mean for MDP2/BioCTL compared to historical results for MDP1/Parma. It is expected that the improvements implemented for the IL5 neutralization bioassay as a result of the investigation will control the occurrences of elevated ED₅₀ ratio values and restore the elevated ED₅₀ ratio mean to a level in line with the historical mean. However, implementation of a (b) (4) control limit will provide additional assurance that acceptable results are produced at BioCTL. This control limit will be implemented temporarily until enough MDP2 batches have been tested with the improved method to be certain that the mean has been restored to the historical level. Note, the upper control limit of \geq (b) (4) will be permanent and is not subject to further evaluation.

QUESTION 2

When the Annual Report is filed, in addition to providing updated stability data, provide a summary of the release results for all drug substance and drug product lots manufactured during the reporting period.

Response

GSK commits to providing batch analysis data for drug substance (DS) and drug product (DP) batches which have been manufactured and released during the reporting period for the first BLA Annual Report. We expect that approximately 20 new batches of DS and DP will be available at that time. For clarity, the IL5 neutralization bioassay is not included on the DS specification, therefore only the DP batch analysis data will include the IL5 neutralization bioassay for new batches. The stability data update will include IL5 neutralization bioassay results for new timepoints from ongoing DS and DP stability studies plus one new annual commitment DP batch.

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/s/

LYDIA I GILBERT MCCLAIN
08/19/2015



BLA 125526

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

GlaxoSmithKline LLC
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Thomas Lampkin, PharmD
Senior Director, Global Regulatory Affairs

Dear Dr. Lampkin:

Please refer to your Biologic License Application (BLA) submitted under the Public Health Service Act for mepolizumab 100 mg SC.

We also refer to the Late-Cycle Meeting (LCM) scheduled for August 6, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Nina Ton, Senior Regulatory Project Manager, at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: August 6, 2015; 12:00 – 1:00 PM EST
Meeting Location: Teleconference
Application Number: 125526
Product Name: Mepolizumab
Indication: Asthma
Applicant Name: GlaxoSmithKline

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues at this time.

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. **Introductory Comments** – 5 minutes

- Welcome, Introductions, Ground rules, Objectives of the meeting

2. **Discussion of Substantive Review Issues**

- No substantive review issues for discussion

3. **Discussion of Minor Review Issues** – 10 minutes

- We reviewed your submission dated July 27, 2015 regarding your investigation into the elevated results in the IL5 Neutralization Assay for MDP2 lots. Overall, we accept the conclusions of your investigation, but would like to discuss two items.
 1. Provide your rationale for including the $(b) (4)$ control limit of an ED50 ratio $\leq (b) (4)$.
 2. When the Annual Report is filed, in addition to providing updated stability data, provide a summary of the release results for all drug substance and drug product lots manufactured during the reporting period.

4. **Additional Applicant Data**

- No new applicant data for discussion

5. **Information Requests**

- No pending Information requests

6. **Postmarketing Requirements/Postmarketing Commitments** – 5 minutes

- Pregnancy Registry – PMR
- PREA – PMR – pediatric study in children 6 to 11 years ongoing; PK/PD study as part of Agency's agreed upon iPSP

7. **Major labeling issues** – 10 minutes

- Labeling comments sent June 24, 2015 and July 2, 2015; updated labeling received July 21, 2015

8. **Review Plans** – 5 minutes

- Reviews ongoing and on target with PDUFA goals

9. Wrap-up and Action Items – 5 minutes

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/s/

BADRUL A CHOWDHURY
07/29/2015