

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761122Orig1s000

OTHER REVIEW(S)



U.S. FOOD & DRUG
ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of assessment:	May 16, 2019
Assessor:	Scott Dallas, RPh, Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Lymarie Maldonado-Baez, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761122
Applicant:	GlaxoSmithKline LLC
Submission Date:	August 7, 2018; February 28, April 18 and May 9, 2019
Product:	Nucala (mepolizumab)
Dosage forms:	Injection
Strength and Container-Closure:	100 mg/mL, single-dose prefilled autoinjector or single-dose prefilled syringe (proposed under BLA 761122)
Purpose of assessment:	The Applicant submitted a biologics license application for a liquid formulation of Nucala (mepolizumab) to be administered subcutaneously via an autoinjector or a safety syringe device.
Recommendations:	The prescribing information, patient information, instructions for use, container labels, and carton labeling are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	Appendix Section
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

DISCUSSION

We evaluated the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations (see Appendix B).

Please note the Prescribing Information for this BLA is to be combined with the approved labeling for BLA 125526 Nucala (mepolizumab) for injection, 100 mg/vial, approved on November 4, 2015.

CONCLUSION

The prescribing information, patient information, instructions for use, container labels, and carton labeling submitted on April 18 and May 9, 2019 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Patient Information (submitted on August 7, 2018)
<\\cdsesub1\evsprod\bla761122\0001\m1\us\114-labeling\1141-draft\draft-annotated.pdf>
- Instructions for Use - Autoinjector (submitted on August 7, 2018)
<\\cdsesub1\evsprod\bla761122\0001\m1\us\114-labeling\1141-draft\draft-auto-ifu-100mg.pdf>
- Instructions for Use - Syringe (submitted on August 7, 2018)
<\\cdsesub1\evsprod\bla761122\0001\m1\us\114-labeling\1141-draft\draft-syr-ifu-100mg.pdf>

(b) (4)



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

Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Commercial and Sample Container Labels

Proper Name <i>(for container of a product capable of bearing a full label)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.50, 21 CFR 201.10 Comment/Recommendation: Autoinjector – acceptable Syringe- acceptable	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (placement of dosage form below the proper name):</i> Comment/Recommendation: Autoinjector - acceptable Syringe - acceptable	☒ Yes ☐ No ☐ N/A
Manufacturer name, address, and license number <i>(for container of a product capable of bearing a full label)</i>	Acceptable
21 CFR 610.60 (a)(2), 21 CFR 201, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e) Comment/Recommendation: Autoinjector - acceptable, but no license number which is acceptable because it's a partial label Syringe - acceptable, but no license number which is acceptable because it's a partial label	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the following qualifying statement "Manufactured by:"):</i> Comment/Recommendation: Autoinjector -NA it's a partial label Syringe - NA it's a partial label	☐ Yes ☐ No ☒ N/A

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per 21 CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

Lot number or other lot identification <i>(container capable of bearing a full label shall bear)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.18, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector – Please verify the lot number will be provided on the label per 21 CFR 610.60(a)(3) and indicate where this information will appear. Syringe- acceptable April 18, 2019: The revised autoinjector container labels include the words “Lot” and “Exp”, and GSK confirmed this information will appear on the label. FDA response: GSK’s revisions are acceptable.	
Expiration date <i>(container capable of bearing a full label shall bear)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - Please verify the expiration date will be provided on the label per 21 CFR 610.60(a)(4) and indicate where this information will appear. Syringe – acceptable April 18, 2019: The revised autoinjector container labels include the words “Lot” and “Exp”, and GSK confirmed this information will appear on the label. FDA response: GSK’s revisions are acceptable.	
<i>Recommended labeling practices (the expiration date appears on all aspects of the package):</i>	☐ Yes ☐ No ☒ N/A
Product Strength	Acceptable
21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - acceptable Syringe - acceptable	
<i>Recommended labeling practices (expression of strength for injectable drugs):</i> <i>Reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176</i> <i>USP General Chapters: <7> Labeling</i>	
Autoinjector – acceptable Syringe – acceptable	☒ Yes ☐ No ☐ N/A

Multiple dose containers <i>(recommended individual dose)</i>	Acceptable
21 CFR 610.60, 21 CFR 201.55	☐ Yes ☐ No ☒ N/A
Statement: "Rx only"	Acceptable
21 CFR 610.60, 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Autoinjector - no Rx only statement, but it's acceptable, because it can be considered a partial label Syringe- no Rx only statement, but it's acceptable, because it can be considered a partial label	
Recommended labeling practices:	☐ Yes ☐ No ☒ N/A
Medication Guide	Acceptable
21 CFR 610.60, 21 CFR 208.24	☐ Yes ☐ No ☒ N/A
No Package for container	Acceptable
21 CFR 610.60	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: <i>(U.S license number for container bearing a partial label)</i>	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: partial label	
No container label	Acceptable
21 CFR 610.60	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Autoinjector - ok, it has a carton Syringe – ok, it has a carton	
Ferrule and cap overseal <i>(for vials only)</i>	Acceptable
Recommended labeling practices: United States Pharmacopeia (USP), General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

Visual inspection <i>(for vials only)</i>	Acceptable
21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector and Syringe – provide an inspection window	
NDC numbers	Acceptable
21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector – acceptable, has a NDC Syringe- acceptable, does not contain a NDC, but it is a partial label	
Route of administration	Acceptable
21 CFR 201.5, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - acceptable Syringe- acceptable, does not contain a ROA, but it is a partial label	
Recommended labeling practices: route of administration statement to appear after the strength statement on the principal display panel	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Autoinjector - space/design does not permit this format Syringe- NA, partial label	
Preparation instructions	Acceptable
21 CFR 201.5	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Autoinjector - not required partial label Syringe – not required partial label	

Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430) Please note OPDP recommended removal of the partial instruction graphics on the container label.	☐ Yes ☐ No ☒ N/A
<u>Package type term</u>	<u>Acceptable</u>
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements</i> Comment/Recommendation: Autoinjector -acceptable Syringe- not required partial label	☒ Yes ☐ No ☐ N/A
<u>Misleading statements</u>	<u>Acceptable</u>
21 CFR 201.6 Comment/Recommendation: Autoinjector -NA Syringe- NA	☐ Yes ☐ No ☒ N/A
<u>Prominence of required label statements</u>	<u>Acceptable</u>
21 CFR 201.15 Comment/Recommendation: Autoinjector - acceptable Syringe- acceptable	☒ Yes ☐ No ☐ N/A
<u>Spanish-language (Drugs)</u>	<u>Acceptable</u>
21 CFR 201.16	☐ Yes ☐ No ☒ N/A
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u>	<u>Acceptable</u>
21 CFR 201.20	☐ Yes ☐ No ☒ N/A
<u>Phenylalanine as a component of aspartame</u>	<u>Acceptable</u>
21 CFR 201.21	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements	Acceptable
21 CFR 201.22	☐ Yes ☐ No ☒ N/A
Bar code label requirements	Acceptable
21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - acceptable Note: The sample autoinjector label does not contain a linear bar code. It displays the phrase "Sample – Not for Sale" Syringe – acceptable Note: The sample syringe label does not contain a linear bar code, which is acceptable for product samples. It displays the phrase "Sample – Not for Sale"	
<i>Recommended labeling practices:</i> <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - acceptable Syringe – not required partial label	
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	Acceptable
21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	
Net quantity	Acceptable
21 CFR 201.51	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - acceptable Syringe - acceptable	
<i>Recommended labeling practices:</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463)</i> <i>Guidance: Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Autoinjector - acceptable Syringe- partial label not required	
Usual dosage statement	Acceptable
21 CFR 201.55, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - partial label not required Syringe – partial label not required	
Inactive ingredients	Acceptable
21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Autoinjector - partial label not required Syringe – partial label not required	
Recommended labeling practices: USP General Chapters <1091> Labeling of Inactive Ingredients	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Autoinjector - partial label not required Syringe – partial label not required	
Storage requirements	Acceptable
<i>Recommended labeling practices:</i> <i>USP General Chapters <7> Labeling</i> <i>USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector – acceptable, includes protect from light, do not freeze or shake, avoid exposure to heat. Syringe – partial label not required	
Dispensing container	Acceptable
21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Autoinjector -ok na Syringe – ok na	

Package⁵ Label Evaluation

Commercial and Sample Carton Labeling

Proper name	Acceptable
21 CFR 610.61, 21 CFR 201.50, 21 CFR 201.10	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Manufacturer name, address, and license number	Acceptable
21 CFR 610.61, 21 CFR 201.1(a), 21 CFR 201.1(h)(5), 21 CFR 201.1(h)(6), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Recommended labeling practices: OPQ-OBP-RP-014	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Lot number or other lot identification	Acceptable
21 CFR 610.61	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Expiration date	Acceptable
21 CFR 610.61, 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - acceptable Syringe – acceptable	

⁵ Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

<u>Preservative</u>	<u>Acceptable</u>
21 CFR 610.61	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector - Please include the statement "No Preservative" per 21 CFR 610.61(e). Syringe – Please include the statement "No Preservative" per 21 CFR 610.61(e). April 18, 2019: GSK included a "No preservative." Statement on the cartons. FDA response: GSK's revision is acceptable.	
<u>Number of containers</u>	<u>Acceptable</u>
21 CFR 610.61	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
<u>Strength/volume</u>	<u>Acceptable</u>
21 CFR 610.61, 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
<i>Recommended labeling practices:</i> <i>Draft Guidance Safety Considerations for Container Labels and Carton Labeling</i> <i>Design to Minimize Medication Errors, April 2013 line 176</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
<u>Storage temperature/requirements</u>	<u>Acceptable</u>
21 CFR 610.61	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	

Autoinjector - Please revise the second paragraph of the patient storage information to read "If necessary" or "If needed" or read "If necessary, NUCALA may be stored outside of the refrigerator up to 86°F (30°C) for up to 7 days in the unopened carton." The phrase may help reinforce that room temperature storage should only be considered a secondary storage condition.

Syringe - Please revise the second paragraph of the patient storage information to include the phrase "If necessary" or "If needed" to read "If necessary, NUCALA may be stored outside of the refrigerator at up to 86°F (30°C) for up to 7 days in the unopened carton." The phrase may help reinforce that room temperature storage should only be considered a secondary storage condition.

April 18, 2019: GSK included a "If necessary" phrase to begin the alternative storage condition on the cartons.

FDA response: GSK's revision is acceptable.

Recommended labeling practices:
USP General Chapters: <7> Labeling

☒ Yes
☐ No
☐ N/A

Comment/Recommendation:

Autoinjector - Please consider including the statement "Write the date removed from the refrigerator ___/___/___." either above or below the sentence "Discard if left out of the refrigerator for more than 7 days." Ensure the area for the date, ___/___/___, is large enough for the patient or caregiver to clearly write the date. The additional statement may help the patient/caregiver determine when the product should be discarded.

Syringe - Please consider including the statement "Write the date removed from the refrigerator ___/___/___." either above or below the sentence "Discard if left out of the refrigerator for more than 7 days." Ensure the area for the date, ___/___/___, is large enough for the patient or caregiver to clearly write the date. The additional statement may help the patient/caregiver determine when the product should be discarded.

April 18, 2019: GSK included the requested sentence on the cartons and there appears to be adequate space to write a date.

FDA response: GSK's revision is acceptable.

Handling: "Do Not Shake", "Do not Freeze" or equivalent

Acceptable

21 CFR 610.61

☒ Yes
☐ No
☐ N/A

Comment/Recommendation:

Autoinjector -acceptable, includes protect from light, do not freeze or shake, avoid exposure to heat. Syringe – acceptable, includes protect from light, do not freeze or shake, avoid exposure to heat.	
Multiple dose containers (recommended individual dose)	Acceptable
21 CFR 610.61 Comment/Recommendation: Autoinjector - na Syringe – na	☐ Yes ☐ No ☒ N/A
Route of administration	Acceptable
21 CFR 610.61, 21 CFR 201.5, 21 CFR 201.100 Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement recommended locations):</i> Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	☒ Yes ☐ No ☐ N/A
Known sensitizing substances	Acceptable
21 CFR 610.61 Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	☐ Yes ☐ No ☐ N/A
Inactive ingredients	Acceptable
21 CFR 610.61, 21 CFR 201.100 Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	☒ Yes ☐ No ☐ N/A

<i>Recommended labeling practices:</i> <i>USP General Chapters <1091> Labeling of Inactive Ingredients</i> <i>USP General Chapters <7> Labeling</i>		☒ Yes ☐ No ☐ N/A
Comment/Recommendation:		
Autoinjector -acceptable Syringe – acceptable		
Source of the product		Acceptable
21 CFR 610.61		☒ Yes ☐ No ☐ N/A
Comment/Recommendation:		
Autoinjector -acceptable Syringe – acceptable		
Minimum potency of product		Acceptable
21 CFR 610.61		☒ Yes ☐ No ☐ N/A
Comment/Recommendation:		
Autoinjector – Please include the statement “No U.S. standard of potency” per 21 CFR 610.61(r). Syringe – – Please include the statement “No U.S. standard of potency” per 21 CFR 610.61(r). March 15 Lynmarie confirmed there is no U.S. standard of potency. April 18, 2019: GSK included a “No U.S standard of potency” statement on the cartons. FDA response: GSK’s revision is acceptable.		
Rx only		Acceptable
21 CFR 610.61, 21 CFR 201.100		☒ Yes ☐ No ☐ N/A
Comment/Recommendation:		
Autoinjector -acceptable Syringe – acceptable		
Recommended labeling practices:		☒ Yes ☐ No ☐ N/A
Comment/Recommendation:		
Autoinjector -acceptable Syringe – acceptable		

Divided manufacturing	Acceptable
21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Distributor	Acceptable
21 CFR 610.64 (Name and address of distributor)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Bar code	Acceptable
21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Recommended labeling practices: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)</i>	☐ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products)	Acceptable
21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: NA	
NDC numbers	Acceptable
21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	

Preparation instructions	Acceptable
21 CFR 201.5 Comment/Recommendation: Autoinjector - na Syringe – na	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430) USP General Chapters <7> Labeling Comment/Recommendation: Autoinjector - na Syringe – acceptable	☐ Yes ☐ No ☒ N/A
Package type term	Acceptable
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use. USP chapter <659> Packaging and Storage Requirements</i> Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	☒ Yes ☐ No ☐ N/A
Misleading statements	Acceptable
21 CFR 201.6 Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	☒ Yes ☐ No ☐ N/A
Prominence of required label statements	Acceptable
21 CFR 201.15 Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	☒ Yes ☐ No ☐ N/A
Spanish-language (Drugs)	Acceptable
21 CFR 201.16 Comment/Recommendation:	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6	Acceptable
21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: NA	
Phenylalanine as a component of aspartame	Acceptable
21 CFR 201.21	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: NA	
Sulfites: required warning statements	Acceptable
21 CFR 201.22	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: NA	
Net quantity	Acceptable
21 CFR 201.51	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Recommended labeling practices: <i>Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463)</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Usual dosage statement	Acceptable
21 CFR 201.55, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	
Dispensing container	Acceptable
21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: Autoinjector -acceptable Syringe – acceptable	

Medication Guide	Acceptable
21 CFR 610.60, 21 CFR 208.24	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: NA	
Other	Acceptable
	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: NA	

Prescribing Information and Patient Labeling Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices: Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry</i>	☒ Yes ☐ No ☐ N/A
DOSAGE AND ADMINISTRATION	Acceptable
<i>Recommended labeling practices: USP nomenclature for diluents and intravenous solutions</i>	☐ Yes ☐ No ☒ N/A
Comment/Recommendation:	
DOSAGE FORMS AND STRENGTHS	Acceptable
21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
<i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in</i>	☒ Yes ☐ No ☐ N/A

Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)
USP chapter <659> Packaging and Storage Requirements
Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176
USP General Chapters: <7> Labeling

Comment/Recommendation:

To Applicant: Please delete the (b) (4) from this section.

May 9, 2019: The applicant deleted the (b) (4) from the Dosage Forms and Strengths section.

FDA Response: The applicant's revisions are acceptable.

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION

Acceptable

21 CFR 201.57(c)(3)(iv)

☒ Yes
☐ No
☐ N/A

Comment/Recommendation :

Dr. Maldonado-Baez confirmed that the (b) (4)

Recommended labeling practices:
USP nomenclature for diluents and intravenous solutions

☒ Yes
☐ No
☐ N/A

Comment/Recommendation:

3 DOSAGE FORMS AND STRENGTHS

Acceptable

21 CFR 201.57(c)(4)

☒ Yes
☐ No
☐ N/A

Comment/Recommendation:

To Applicant: Please delete the (b) (4) from this section.

The comment applies to both the powder and the solution.

To Applicant: Please include a description of the identifying characteristics per 21 CFR 201.57(c)(4). Please ensure the identifying characteristics in section 3 and 16 are consistent.

Dr. Maldonado-Baez confirmed the identifying characteristics for the powder are "white to off-white" and for the solution are "clear to opalescent, colorless to pale yellow to pale brown".

May 9, 2019: The applicant deleted the (b) (4) and added the identifying characteristics for the "for injection" and "injection" dosage formulations.

FDA Response: The applicant's revisions are acceptable.

<i>Recommended labeling practices:</i> <i>Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)</i> <i>USP General Chapters <659>, USP General Chapters <7></i> Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
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11 DESCRIPTION	Acceptable
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21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q) Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
--	---

Dr. Maldonado-Baez confirmed the information in the first and second paragraphs is correct (e.g., the cell line-CHO, MW, (b) (4), ingredient qualitative and quantitative info, sterile, preservative-free, and pH). Dr. Maldonado-Baez also confirmed neither the vial, autoinjector or syringe are made with natural rubber latex.

<i>Recommended labeling practices:</i> <i>USP General Chapters <1091>, USP General Chapters <7></i> Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
---	---

16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
--	-------------------

21 CFR 201.57(c)(17) Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
---	---

For injection: To Applicant: Included the identifying characteristic of color.

Injection: To Applicant: Include "to pale brown" as part of the identifying characteristics.

May 9, 2019: The applicant revised the identifying characteristics as requested.

FDA Response: The applicant's revisions are acceptable.

Dr. Maldonado-Baez confirmed the product should be refrigerated, protect from light until time of use, do not freeze or shake, avoid exposure to heat. Dr. Maldonado-Baez confirmed the stability data is acceptable for the statements "If necessary, an unopened carton can be stored outside the refrigerator at up to 86°F (30°C) for up to 7 days. Discard if left out of the refrigerator for more than seven days." And stability and expose to light studies support that "NUCALA injection must be administered within 8 hours after removal from the carton. Discard if not administered within 8 hours."	
<i>Recommended labeling practices (placement of detailed storage conditions for reconstituted and diluted products):</i> Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
MANUFACTURER INFORMATION	
21 CFR 610.61, 21 CFR 610.64, 21 CFR 201.1, 19 CFR 134.11 Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
Recommended labeling practices: Comment/Recommendation:	☒ Yes ☐ No ☐ N/A
PATIENT INFORMATION LABELING, and INSTRUCTIONS FOR USE (prefilled syringe and autoinjector)	
TITLE (NAMES AND DOSAGE FORM)	
Regulation for Medication Guide: 21 CFR 208.20(a)(7) Comment/Recommendation: Patient Information: acceptable Instructions for Use: acceptable Recommended Labeling Practice Comment:	☒ Yes ☐ No ☐ N/A
STORAGE AND HANDLING	
<i>Recommended labeling practices (ensure consistency with prescribing information):</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:	
Patient Information: acceptable Instructions for Use: acceptable	
INGREDIENTS	Acceptable
<i>Recommended labeling practices: USP General Chapters <1091>: Labeling of inactive ingredients in alphabetical order</i>	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Patient Information: acceptable Instructions for Use: To Applicant: Revised the clarity and color to be consistent with the identifying characteristics in the PI.	
May 9, 2019: The applicant revised the identifying characteristics to include "pale brown" in the Instructions for Use.	
FDA Response: The applicant's revision is acceptable.	
MANUFACTURER INFORMATION	Acceptable
21 CFR 610.61, 21 CFR 610.64, 21 CFR 201.1, 19 CFR 134.11 21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
Comment/Recommendation:	
Patient Information: acceptable Instructions for Use: acceptable	

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information and Patient Information (submitted on May 9, 2019)
<\\cdsesub1\evsprod\bla761122\0032\m1\us\114-labeling\1141-draft\draft-clean.doc>
- Instructions for Use - Autoinjector (submitted on May 9, 2019)
<\\cdsesub1\evsprod\bla761122\0032\m1\us\114-labeling\1141-draft\draft-cleanifu-autoinjector.docx>
- Instructions for Use - Syringe (submitted on May 9, 2019)
<\\cdsesub1\evsprod\bla761122\0032\m1\us\114-labeling\1141-draft\draft-cleanifu-syringe.docx>



Scott
Dallas

Digitally signed by Scott Dallas
Date: 5/17/2019 01:16:58PM
GUID: 508da712000294048aa136a18a6af06a



Lymarie
Maldonado-Baez

Digitally signed by Lymarie Maldonado-Baez
Date: 5/17/2019 05:11:14PM
GUID: 5ac7de300070e5e69fb599e6b33f405e

OFFICE OF DEVICE EVALUATIONDIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date	May 10, 2019
To	Bamidele Aisida CDER/OPQ/OBP
Requesting Division	DPARP
From	Sapana Patel PharmD. CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	Sarah Mollo Ph.D. CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # BLA 761122 ICCR # 2018-03453 ICC# 1800689
Recommendation	• Device Constituent Parts of the Combination Product are Approvable with PMCs APPROVAL OF THE DEVICE CONSTITUENTS FOR THE PREFILLED SYRINGE WITH SAFETY SRYINGE DEVICE (b) (4) APPROVAL OF THE DEVICE CONSTITUENT FOR THE AUTOINJECTOR with the following PMC for the sponsor to provide the following: Provide dose accuracy, injection time and activation force for the remaining 18 month and 24 month timepoints for ongoing stability protocol on the three Aged PPQ YpsoMate batches used to verify of the autoinjector functionality after aging with the final report submission by January 31, 2020.

Digital Signature Concurrence Table	
Reviewer	Sapana Patel -S Digitally signed by Sapana Patel -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sapana Patel -S, 0.9.2342.19200300.100.1.1=2001554957 Date: 2019.05.10 20:50:31 -04'00'
Team Lead	
Branch Chief	 Alan M. Stevens -S

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1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICCR 2018-03453
ICCR SharePoint Link	http://sharepoint.fda.gov/
ICC tracking # (Lead)	ICC 1800689
Submission Number	BLA 761122
Sponsor	GlaxoSmithKline LLC
Drug/Biologic	Mepolizumab
Indications for Use	Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA). (b) (4)
Device Constituent	Autoinjector (AI) Safety Syringe Device (SSD)
Related Files	PIND (b) (4) /IND 006971 ICC1600635 ICC1066126 ICC1800280

Table 2. Review Team	
CDER/CBER Lead Review Division	Division of Pulmonary, Allergy, and Rheumatology Products
Submission RPM	Bamidele Aisida
Lead Device Reviewer	Sapana Patel PharmD.
The CDRH review is being managed under ICC #: ICC1800689	
Below is a list of the Discipline Specific	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)
Engineering	Jacqueline Gertz
Compliance	Payal Patel

Table 3. Important Dates		
1st round of Information Requests	11/29/2018	
2nd Round of Information Requests	1/15/2019, 2/12/2019	
Interim Due Dates	Meeting Date	Due Date
Filing	9/12/2018 (CMC)	
Mid-Cycle	1/8/2019	
Primary Review		4/22/2019

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2. PURPOSE/BACKGROUND

2.1. Scope

GlaxoSmithKline LLC(GSK) has submitted a new Biologics License Application for the liquid formulation of NUCALA(Mepolizumab) to be administered subcutaneously (SC) via an Autoinjector (AI) or a Safety Syringe Device (SSD). The liquid Mepolizumab is intended to simplify the preparation and administration of Mepolizumab by not requiring reconstitution at the point of care, and the devices will allow for admission by the patient or caregiver outside of the healthcare setting.

The currently approved product, Nucala (Mepolizumab), is supplied as a lyophilized powder(100 mg) that requires reconstitution before being administered subcutaneously (SC) only in a health care setting. Nucala is indicated for Severe Asthma and Eosinophilic Granulomatosis with Polyangiitis (EGPA) in the United States under BLA 125526.

This submission contains supporting bridging data to demonstrate comparable systemic exposure to the lyophilized product when liquid Mepolizumab is administered via AI or SSD, and assurance around the effective, consistent use of the devices in a representative patient population using focused, stand-alone real-world use and human factor studies.

The dose (100mg), dosage form (a liquid, administered to the patient) and the route of administration (subcutaneous) between the approved product (BLA 125526) and liquid Mepolizumab are the same. The active drug substance, Mepolizumab, and the route of administration, subcutaneous injection, are qualitatively and quantitatively unchanged.

The scope of this review covers:

- Device Performance of the Autoinjector and Safety Syringe Device
- Release Specifications

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Human Factors
- Sterility
- Biocompatibility of the Fluid Path

2.2. Prior Interactions

The sponsor had 4 meetings with the Agency prior to this submission.

Type B Pre-IND Meeting (PIND (b) (4))
Type C Pre-IND Meeting (PIND (b) (4))
Type B Pre-BLA Meeting (IND 006971)
Type C CMC Only Written responses

2.2.1. Related Files

ICC1600635
ICC1066126
ICC1800280

2.3. Indications for Use

Combination Product	Indications for Use
---------------------	---------------------

Mepolizumab (NUCALA)	Currently Approved Indications: - Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. - The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).
Autoinjector (b) (4)	For Administration of Drug
Prefilled Syringe with Safety Syringe Device (b) (4) provided	(b) (4) - Single use devices that are indicated for use as an accessory with pre-filled ISO Standard glass syringes to aid in the protection of healthcare professions, patients who self-inject doctor prescribed medications and individuals that assist self-injecting patients, from accidental needle sticks. The intended patient population is unrestricted and may include children and adults, and parental methods of administration. Additionally, the (b) (4) device is designed with a larger viewing window indicated where pharma company offering is a low volume and instructions request visualization. The (b) (4) device is designed with a robust plunger and built in extended finger flanges indicated where pharma customer offering is viscous. Syringe- For administration of Drug

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
2.4.4 Container Closure System Development - Autoinjector	3.2.P.2.4.4
2.4.5 Container Closure System Development - Safety Syringe	
3.2.P.3.5. Process Validation and/or Evaluation	
Process Validation and/or Evaluation	
3.2.P.7. Container Closure System	3.2.P.7
- Container Closure System - Description - Container Closure System - PFS - Container Closure System - Autoinjector - Container Closure System - Safety Syringe	
- Draft Labeling Text - Proposed - MS Word - Original BLA - Draft Labeling Text - Clean - MS Word - Original BLA - Draft Patient Instructions - Clean - Autoinjector - MS Word - Original BLA - Draft Patient Instructions - Clean - Syringe - MS Word - Original BLA	1.14.1.3
3.2.P.8.3. Stability Data	
Stability Data	
27Feb2018 - FDA Meeting Minutes Type B Pre-BLA meeting	1.6.3
CMC Responses to FDA Questions Dated 29Nov2018	1.11

 3.2.R Attachment_2018N367407 SSD ISO Verification Test Report  3.2.R Attachment_2018N367440 SSD Functional Test Report  3.2.R Attachment_2018N367456 Functional testing after ASTM shipping simulations  3.2.R Attachment_2018N369526 Functionality Test Report on Aged PPQ BD UltraSafe Plus Safety Syringe Devices	3.2R
 3.2.P.8.1. Stability Summary and Conclusion  Stability Summary and Conclusions	

4. FILING REVIEW FILING REVIEW

CDRH performed Filing Review	X
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☐

Filing Recommendation	
Filing Information Requests	Section 11.1 Filing IRs - # Section 11.2 74-Day-letter IRs - #
The device constituent content in the submission for the combination product is acceptable for filing	☐
The device constituent content in the submission for the combination product is acceptable for filing, CDRH has Information Requests to include in the 74-Day letter, See Section 11.2	☐
The device constituent content in the submission for the combination product is acceptable for filing, See Section 11.1 for Filing Information Requests	☐

5. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

This information was taken for Section 3.2.P.7 Container Closure System

The container closure system for Mepolizumab Injection, 100 mg/mL is composed of a prefilled syringe (PFS) as the primary container which is assembled into an autoinjector or a safety syringe device. An overview of the design and operation of these devices is provided in Section P.2.4 Container Closure Introduction. The devices comply with the relevant requirements set forth by ISO 11608-1 and ISO 11608-5.

The PFS is composed of a 1 mL long USP Type (b) (4) glass barrel (b) (4) with staked 29G x ½" thin-wall (TW) needle and rigid needle shield (RNS) that is preassembled onto the syringe. The RNS is composed of a (b) (4) (b) (4) insert and (b) (4) outer cover. After (b) (4)

The autoinjector consists of two subassembly components (syringe unit and drive unit) that are assembled together with the PFS. The safety syringe consists of three components (needle guard, plunger rod, and a finger flange) which are assembled together with the PFS. In all formats, however, the drug product contacts only the prefilled syringe components and is not in direct contact with the autoinjector or safety syringe subassembly components.

LOAs were provided for the following:

Letters of Authorization provided in this document

Reference Number	Product	Supplier
DMF (b) (4)		(b) (4)
K (b) (4)		
DMF (b) (4)		
MAF (b) (4)		

¹ A list of depyrogenation and sterilization sites follows the Letter of Authorization

Pre-Filled Syringe (Taken from 3.2.P.7 Container Closure System PFS)

The primary container closure (prefilled syringe) for Mepolizumab Injection, 100 mg/mL for commercial use is identical to the prefilled syringe used in clinical trials (studies 205958, 204959, and 205667). The prefilled syringe consists of the components listed in [Table 1](#).

Table 1 Primary Container Closure - Syringe Materials and Function

Component	Subcomponent	Supplier	Material Description	Color	Function
Syringe	(b) (4)				
Plunger stopper	(b) (4)				

Note:

Abbreviations: (b) (4) Rigid Needle Shield (RNS); (b) (4) Thin-wall (TW)

Table 1 Prefilled Syringe (Primary Container Closure) Input Components

Component Name / Description	Supplier
1 mL long syringe barrel with 29Gx1/2" TW staked needle and rigid needle shield (RNS) preassembled on the syringe (b) (4)	(b) (4)
plunger stopper, (b) (4)	

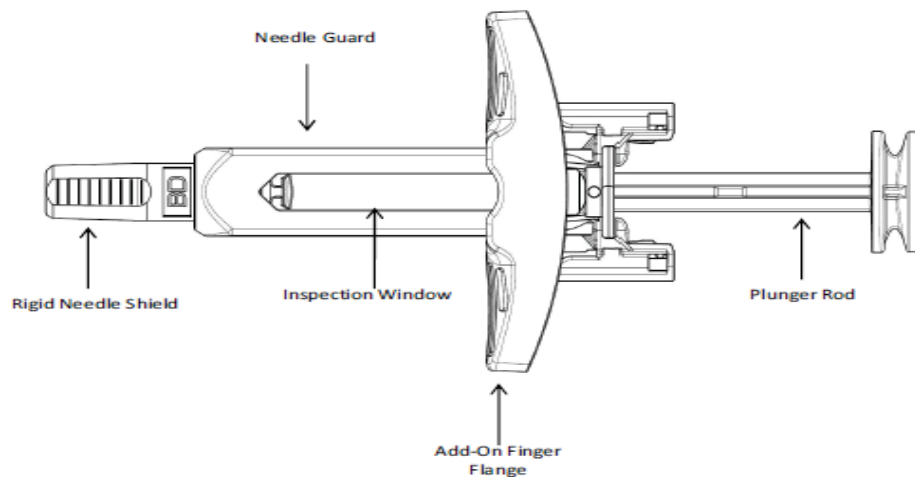
Figure 1 Representative Drawing of the (b) (4) Syringe Barrel with RNS Preassembled



Safety Syringe (Taken from Section 3.2.P.7 Safety Syringe)

The safety syringe device has been developed by (b) (4) The safety syringe device is a single-use, disposable device designed to enable manual delivery of Mepolizumab by a patient, caregiver or healthcare professional, while providing a needle shielding feature (post-use) and enhanced ergonomics. The safety syringe employs the Pre-Filled Syringe (PFS) as the primary container closure described in P.2.4 Container Closure System_PFS. The safety syringe

device utilizes commercially available components specifically designed for prefilled syringes. These components include a needle guard, which is a passive anti-needle stick device possessing 510k clearance (#K (b) (4) in the United States and CE marking in Europe as described below. The overall dimensions of the safety syringe device are (b) (4) mm as illustrated in Figure 1. An overview of the operation of the safety syringe device is described in Section P.2.4 Container Closure Safety Syringe. The individual components of the device are manufactured by (b) (4) which are provided to GSK for final assembly with the PFS.



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Table 1 Materials of Construction for Safety Syringe Components

Subassembly Component	Individual Component Name	Material of Construction	Color	Function
Needle Guard	Body ¹	(b) (4)		
	Guard ¹			
	Spring			
Plunger Rod ¹	Not Applicable			
Finger Flange ¹	Not Applicable			

Notes:

1. Component with potential patient contact and therefore subjected to biocompatibility testing.

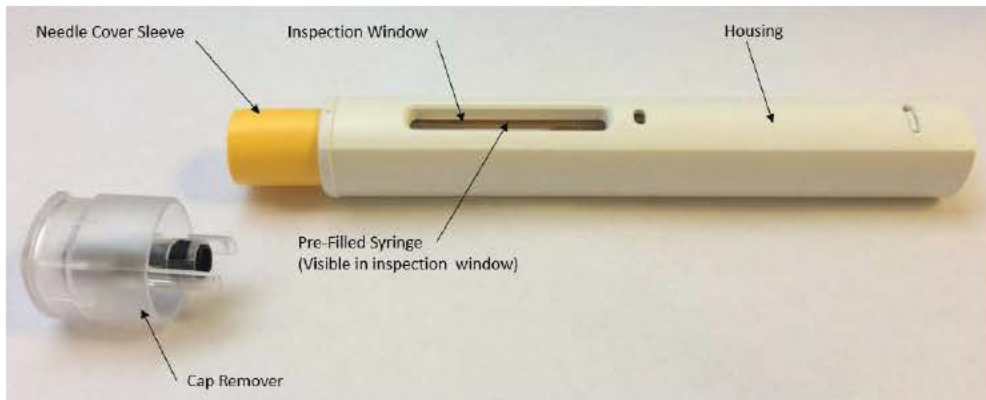
Syringe Device Description - PFS

Device Characteristic	N/A	Description / Specification
Syringe Name		(b) (4) Syringe + (b) (4) Passive Needle Guard
Syringe Platform Name (if applicable)	X	
Priming Dose / Volume	X	
Dose accuracy		(b) (4) ml
Injection Time	X	Manual Injection
Injection Site		Subcutaneous
Injection tissue and depth of injection		Arms, Abdomen
Audible / visual feedback		Visual
Cap Removal Force		(b) (4) N
Activation Force		(b) (4) N (Needle Guard Activation Force)
Visibility of medication container		Clear Container w/ 100% visibility
Needle Guard Override Force		> (b) (4) N
Needle Specifications • Length(s) • Gauge(s) • Connection type ○ ISO 11608-2:2012 ○ Prestaked		29G Thin Wall (TW) x ½ inch needle Staked Needle (b) (4) stainless steel

Device Characteristic	N/A	Description / Specification
Type of Use (e.g. single use, disposable, reusable, other)		Single Use
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)		Self-Administer
Method of actuation		Manual (for injection) Passive (Needle Safety feature)
Automated Functions		Needle Safety feature
Residual Medication	X	
Drug Container Type		USP Type (b) (4) glass
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	X	
Environments of use		Home Use
Storage conditions and expiry		Refrigerated 2°-8° 24 month shelf life
Graduation marks / fill lines	X	Single Dose
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.		➤ Prior to using the safety syringe, the device must sit outside of the refrigerator for 30 minutes to allow the solution to come to room temperature. To perform the injection, the user first removes the needle cap (rigid needle shield) by pulling it straight off. ➤ The user pinches a fold of skin and inserts the entire needle into the pinched area of the skin at a slight angle (approximately 45°). ➤ The user then manually pushes the plunger rod down until all the solution in the prefilled syringe is expelled. The user can monitor the progress of the injection by looking at the white plunger rod in the window. The end of injection is determined when the plunger stopper is at the bottom of the syringe and the user cannot push the plunger rod any further. ➤ Upon completion of the injection and slowly releasing pressure on the plunger rod (by slowly moving the thumb back), the needle will automatically retract into the needle guard and lock so that the needle is shielded. ➤ The user removes the safety syringe away from the injection site and disposes of it in an appropriate sharps container.
Safety Features • Needle safety		(b) (4) Passive Needle Guard
Material composition of PFS		Type (b) (4) Glass

Autoinjector Configuration (Taken from Section 3.2.P.7 Container Closure System Autoinjector)

The autoinjector has been developed by (b) (4). The autoinjector is a single-use, disposable device designed to provide a convenient and safe means for self-administration of Mepolizumab by a patient or through a caregiver or healthcare professional. The autoinjector employs the Pre Filled Syringe (PFS) as the primary container closure described in P.7 Container Closure System_PFS.



The autoinjector consists of 2 subassemblies- the Drive Unit and the Syringe Unit. (b) (4) which are provided to GSK for final assembly with the PFS. These subassembly units are nested together for shipping to the GSK site for final assembly.

Figure 2 Exploded Assembly Diagram of Autoinjector Device



Table 1 Materials of Construction for Autoinjector Components

Subassembly Component	Individual Component Name	Material of Construction	Color	Function
(b) (4)				

Note:

1. Component with potential patient contact and therefore subjected to biocompatibility testing.

Autoinjector Device Description –

Device Characteristic	N/A	Description / Specification
Syringe Name		(b) (4) Prefilled Syringe (same as Safety Syringe)
Autoinjector Platform Name (if applicable)		(b) (4)
Priming Dose / Volume		1.0mL, single fixed dose
Dose accuracy		(b) (4) ml
Injection Time		(b) (4) sec
Injection Site		Arm, Abdomen, Thighs
Injection tissue and depth of injection		Subcutaneous
Audible / visual feedback		Visual feedback: Window turns yellow when injection is done Audible feedback: click sound at beginning and end of injection
Cap Removal Force		(b) (4) N
Injection Actuation Force		(b) (4) N
Needle Safe Distance		(b) (4) mm
Needle Guard Override		(b) (4) N
Visibility of medication container		AI has window to view medication
Needle Extension		(b) (4) mm
Needle Specifications • Length(s) • Gauge(s) • Connection type ○ ISO 11608-2:2012 ○ Prestaked		29G Thin Wall (TW) x ½ inch needle
Type of Use (e.g. single use, disposable, reusable, other)		Single use

Device Characteristic	N/A	Description / Specification
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)		Self-Administer
Method of actuation		Remove RNS cap, press onto injection site
Automated Functions	X	
Residual Medication		No specification
Drug Container Type		Prefilled container closure-Type (b) (4) glass
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	X	
Environments of use		Home use
Storage conditions and expiry		Refrigeration 2°-8° 24 month shelf life
Graduation marks / fill lines	X	
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.		Prior to using the autoinjector, the device must sit outside of the refrigerator for 30 minutes to allow the solution to come to room temperature. To perform the injection, the user first removes the cap. The user then positions the cover sleeve straight onto the injection site. The injection is started by pressing the autoinjector all the way down onto the injection site and holding it in place. This will manually insert the needle (target 5 to 8 mm depth) and start drug delivery. An audible "click" and movement of the yellow indicator in the inspection window signal the start of the injection. The user continues to hold the autoinjector down until a second "click" and the yellow indicator reaches the end of the viewing window and stops moving. When the injection is complete, the user counts to 5 and then lifts the autoinjector from the injection site. The cover sleeve will automatically move back over the needle and lock in place. The user then disposes of the autoinjector in an appropriate sharps container.
Safety Features • Needle safety		Before activation: needle is hidden and retracted before activation After activation: Opaque needle cover extends past the needle and permanently locked in place.
Material composition of PFS		Type (b) (4) glass

Letters of Authorization provided in this document

Reference Number	Product	Supplier
DMF (b) (4)		(b) (4)
K (b) (4)		
DMF (b) (4)		
MAF (b) (4)		

Reviewer Comment: The sponsor provided LOAs for the components of the device constituent. The sponsor provided adequate information regarding the design of the device constituents of the proposed drug product. The sponsor provided adequate device information. Further analysis of the design verification are located within this review memo in Section 8.

6. DESIGN CONTROL REVIEW**6.1. Design Review Summary**

(b) (4)

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

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

Standards for development:

- ☐ ISO 11608-1, Needle-based injection systems for medical use – Requirements and test methods - Part 1: Needle-based injection systems
- ☐ ISO 11608-5, Needle-based injection systems for medical use – Requirements and test methods - Part 5: Automated functions
- ☐ Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products, Guidance for Industry and FDA Staff, June 2011
- ☐ ISO 14971:2007, Application of Risk Management to Medical Devices
- ☐ ISO 23908:2011, Sharps Injury Protection – Requirements and test methods

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)	X			Jacqueline Gertz (Autoinjector Review)		

7.2. Design Validation Review

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

The safety syringe devices used in the clinical trials and human factors studies were the commercial device formats. The autoinjectors used in the clinical studies and formative human factors studies were manufactured from (b) (4), whereas the commercial versions manufactured from (b) (4) were used for summative human factors studies and are intended for commercial use. The fit, form and function of the autoinjector remains unchanged between the clinical and commercial formats. Design verification testing has been conducted throughout the development process to demonstrate compliance with design input requirements on the to be marketed presentation. Human factors summative studies have been conducted on the commercial devices of the safety syringe device and the autoinjector to demonstrate the usability by the target patient population. Following human factors validation, minor updates were made to the IFU that do not impact readability or device use instructions.

Table 1 Tabular Listing of All Mepolizumab Liquid Clinical Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
Pharmacokinetic/Pharmacodynamic Studies						
204958 (2017N342446_01)	PK/PD Safety and Tolerability Immunogenicity Safety syringe and autoinjector use	R, OL, PG	Healthy subjects	Mepolizumab 100 mg SC liquid drug product, single dose either in autoinjector or safety syringe Mepolizumab 100 mg SC lyophilised powder for solution for injection, single dose.	Autoinjector 79/79 Safety syringe 80/80 Lyophilised powder 85/84	Completed/ Reported (CPSR)
Efficacy and Safety Studies: Controlled Clinical Studies Using Liquid						
(b) (4)						
Real World Use and Safety Studies: Uncontrolled Clinical Studies						
204959 (2017N349209_00)	Autoinjector use PK/PD Asthma exacerbations Safety and Tolerability Immunogenicity	OL, RWU	Severe eosinophilic asthma	Mepolizumab 100 mg SC liquid drug product Q4W for 12 weeks self-administered by the subject (or their caregiver) using an autoinjector.	159/157 ^a	Completed/ Reported (CSR)
205667 (2017N331753_00)	Safety syringe use PK/PD Asthma exacerbations Safety and Tolerability Immunogenicity	OL, RWU	Severe eosinophilic asthma	Mepolizumab 100 mg SC liquid drug product Q4W for 12 weeks self-administered by the subject (or their caregiver) using a safety syringe.	56/55	Completed/ Reported (CSR)

a. 19 subjects enrolled and received study medication in both 205667 and 204959. In all cases, subjects first participated and completed Study 205667 before enrolling in Study 204959.

Abbreviations: CPSR= Clinical Pharmacology Study Report; CSR=Clinical Study Report; DB = Double-blind; HCP = Healthcare Professional; mg = milligram(s); OL=Open Label; PC = Placebo-controlled; PD = Pharmacodynamic; PG = Parallel Group; PK = Pharmacokinetic; Q4W=once every 4 weeks; R = Randomised, RWU = Real-world Use, SC = Subcutaneous(ly).

Two different drug product presentations have been used in clinical studies, a prefilled syringe assembled into an autoinjector and a prefilled syringe assembled into a safety syringe device.

Formulation Component	Mepolizumab for Injection Drug Product Presentation
	Clinical and Proposed Commercial
	100 mg/mL syringe ¹ assembled into an autoinjector or a safety syringe device
Clinical Studies	204958 ² 204959 ³ 205667 ⁴

Pharmacokinetic (PK) Study (204958-Autoinjector)

A clinical pharmacokinetic comparability study was conducted on 244 healthy subjects who were administered a single Mepolizumab subcutaneous dose of 100 mg by a health care provider (HCP) either with an autoinjector, safety syringe device or with reconstituted lyophilised drug product from the vial. A total of 79 subjects were administered medication with the autoinjector. This study demonstrated comparable systemic exposure to the lyophilized drug product when the liquid formulation of Mepolizumab is administered via autoinjector or safety syringe device. Secondary PK and pharmacodynamic (PD) parameters were consistent across the 3 treatment groups and consistent with those observed previously in healthy subjects.

No incidents, near incidents or malfunctions were reported with the use of the autoinjector manufactured or marketed, by GSK or by a third party for GSK, for this study (Source Data: Listing 32 from 204958). In addition, no user or device errors were reported for the safety syringe or autoinjector and all doses were successfully administered.

The safety profile of Mepolizumab liquid drug product delivered via autoinjector was consistent with the known safety profile of the lyophilised drug product with no new safety concerns. The details of this study can be found in Section [m.2.7.2](#).

Pharmacokinetic (PK) Study (204958-Safety Syringe)

A clinical pharmacokinetic comparability study was conducted on 244 healthy subjects who were administered a single Mepolizumab subcutaneous dose of 100 mg by a health care provider (HCP) either with an autoinjector, safety syringe device or with reconstituted lyophilised drug product from the vial. A total of 80 subjects were administered medication with the safety syringe device. This study demonstrated comparable systemic exposure to the lyophilized drug product when the liquid formulation of Mepolizumab is administered via autoinjector or safety syringe device. Secondary PK and pharmacodynamic (PD) parameters were consistent across the 3 treatment groups and consistent with those observed previously in healthy subjects. No incidents, near incidents or malfunctions were reported with the use of the safety syringe or autoinjector manufactured or marketed, by GSK or by a third party for GSK, for this study (Source Data: Listing 32 from 204958). In addition, no user or device errors were reported for the safety syringe and all doses were successfully administered. The safety profile of Mepolizumab liquid drug product delivered via safety syringe was consistent with the known safety profile of the lyophilised drug product with no new safety concerns. The details of this study can be found in Section [m.2.7.2](#).

Reviewer Comments: Two different drug product presentations were used in the clinical studies; both the autoinjector and safety syringe device presentations were used for the clinical studies. There were no concerns related to the device in the clinical studies performed. There were no reported incidents reported with the use of the autoinjector or prefilled syringe. The sponsor also provided real world use clinical study demonstrating the device is used reliably with the intended user population. No use errors or device failures were reported by the staff.

Human Factors Validation (Safety Syringe)

The full report for human factors validation of the safety syringe is provided in Section 3.2.R with a summary provided below. The main objectives of the human factors validation study were to:

Demonstrate that the safety syringe, associated IFU, packaging and labelling can be used safely and effectively by intended users without patterns of preventable use errors that may result in harm or reduction in therapeutic efficacy to a patient or user.

Identify any aspects of the safety syringe design, injection procedure or IFU which may lead to confusion, failures, high-risk errors or patient safety risks.

Validate the safety syringe design and IFU as successful in enabling safe and effective use of the device while mitigating high risks in representative use environments with intended users.

To achieve these objectives, a simulated use human factors study was conducted. The study was designed in accordance with FDA Draft Guidance for Industry, "Applying Human Factors and Usability Engineering to Medical Devices". The HF protocol and IFU were reviewed by the FDA and agency feedback was incorporated prior to conducting the study. The study included a total of 90 participants considered to be representative users of the Mepolizumab safety syringe. These participants were divided into the following user groups:

30 Juvenile Asthma Patients, half of whom (n=15) received representative training on device use while the other half self-trained by using the materials provided in the representative product pack.

15 Adult Asthma Patients, who self-trained by using the materials provided in the representative product pack.

15 Caregivers, who self-trained by using the materials provided in the representative product pack.

30 COPD Patients, half of whom (n=15) received representative training on device use while the other half self-trained by using the materials provided in the representative product pack.

All trained subjects participated in two study sessions. During their first study session, they received training on how to use the device and performed a single supervised injection. During their second session, they performed an unaided injection trial, answered knowledge probes and provided feedback on the IFU.

All untrained subjects participated in a single study session. During their study session, they self-trained by familiarizing themselves with the device and IFU, answered a series of knowledge probes, performed an unaided injection and provided feedback on the IFU. During the unaided injections, subjects were observed for their ability to complete critical user tasks which were predefined and categorized based on risk. In addition to the predefined user tasks, the subjects were observed for unanticipated use errors. As summarized in Table 5, the results of the study showed that all participants (90/90, 100%) successfully prepared and carried out the full injection procedure. There were no patterns of (preventable) failures or use errors observed.

Table 5 Summary of Successful Injections from Human Factors Validation Study

Number of Attempted Injections	Number of Successful (Injections)	Proportion (%) of Injections that were Successful	Reported Reasons for Unsuccessful Injections	
			Use	Device failure
90	90	100%	0	0

Based on the results of the human factor validation study, it was demonstrated that the safety syringe, associated IFU, packaging and labelling can be used safely and effectively by intended users.

Human Factors validation was performed on the safety syringe and autoinjector. There were no unsuccessful injection reported during use. The full review of the human factors studies is deferred to DMEPA.

7.3. Design Verification Review (3.2.P.2 Pharmaceutical Development)

7.3.1. Safety Syringe Design Verification (3.2.P.2.4.5 Container Closure Development Safety Syringe)

To demonstrate that the resulting design of the safety syringe device (assembled with the Mepolizumab syringe) achieved the design intent (design input requirements), formal design verification testing was performed by GSK. The safety device components including (b) (4) Needle Guard are commercially available and already possess 510k clearance in the U.S. and CE marking in Europe, therefore, verification testing focused on requirements considered specific to the combination of the device components with Mepolizumab prefilled syringe.

Design Verification Testing Summary (PFS)

A summary of the Functional Performance and Safety Syringe Design Verification was provided in 3.2.P.2.4.5 and provided below:

Functional Performance Parameters for the Safety Syringe

Functional Parameter	Criteria	Basis for Requirement
Cap (rigid needle shield) Removal Force (Linear)	(b) (4)	Usability / human factors
Actuation Force (peak)		Usability / human factors
Needle Extension		Clinical input to ensure subcutaneous injection
Needle Guard Override Force		Safety (ISO 23908)
Delivered Volume (Dose Accuracy)		Clinical input to ensure full dose delivered (ISO 11608)
Needle guard lockout		Safety (ISO 11608)
Needle safe distance		Safety (ISO 23908) The tip of the needle should not be contactable after use (i.e., after lock out).
Break loose force (peak)		Usability / human factors
Glide Force (peak)		Usability / human factors

Table 4 Safety Syringe Design Verification - Functional Performance Data (Standard Conditions) (Section 3.2.P.2.4.5)

Table 4 Safety Syringe Design Verification - Functional Performance Data (Standard Conditions)

Functional Parameter	Acceptance Criteria	Results Average (Min, Max)	Pass/Fail
Cap (rigid needle shield) Removal Force (linear)	(b) (4)		Pass
Actuation Force (Peak)			Pass
Needle Guard Override Force			Pass
Delivered Volume (Dose Accuracy)			Pass
Needle guard lockout			Pass
Needle extension			Pass
Needle safe distance			Pass
Break loose force (peak)			Pass
Glide Force (peak)			Pass

Design verification data for the Safety Syringe Device:

Section m3.2.P.2.4 Container Closure Safety Syringe contains a summary of the testing design input requirements are satisfied. The following reports have been provided with this submission:

(b) (4)
 SSD ISO Verification Test Report
 SSD Functional Test Report
 Functional testing after ASTM shipping simulations
 Functionality Test Report on Aged PPQ

Table 3 Safety Syringe Design Verification

Design Requirement	Reference to ISO Standard	Method of Verification	Design Feature/Results	Conformance with Requirement
The container holder shall allow visibility of the deliverable volume.	ISO11608-1:2014 Section 5.5	Visual inspection and review of component drawings	The (b) (4) Assembly) has a sufficiently large window, allowing the user to inspect the drug product prior to, and during the injection.	Yes
The state of the device, when ready to deliver the dose, shall be different from its state when the dose has been delivered	ISO11608-1:2014 Section 5.5 ISO11608-5:2012 Section 4.1	Visual inspection	The plunger position of an unused device is visible through the window, at the top of the PFS barrel. At the end of the injection, the plunger is at the bottom of the barrel. The (b) (4) lockout mechanism involves the release of the safety spring, resulting in the retraction of the syringe into the device body. This visual indication that the full dose has been delivered differentiates the device from an unused injection.	Yes
It should be evident by visual and audible and/or tactile means to the users when the injection is complete and the device has locked out	ISO11608-1:2014 Section 5.5 ISO11608-5:2012 Section 4.1	Visual inspection	The (b) (4) body assembly ((b) (4) Assembly) has a large window, allowing the user to visually inspect the pre-filled syringe and assess whether the plunger rod fills the window to indicate the completion of the injection. In addition, an opaque (white) plunger rod provides strong contrast so that the position of the plunger rod in the safety syringe (and therefore progress of the injection) can be monitored. Furthermore, when pushing the plunger rod to the end of syringe barrel, the tactile feedback from reaching the end of barrel will indicate the end of injection.	Yes

Design Requirement	Reference to ISO Standard	Method of Verification	Design Feature/Results	Conformance with Requirement
The Safety Syringe shall be designed to avoid unintended activation of the safety mechanism.	ISO11608-5:2014 Section 4.1	Visual inspection	To cause activation of the safety mechanism, a force must be applied to the activation fingers (internal feature of the SSD). This therefore prevents unintended activation. Presence of the activation finger flanges can be confirmed in the supplier component drawings.	Yes
The Safety Syringe should not compromise container (e.g.: DP quality) and/or needle sterility.	ISO11608-5:2014 Section 4.1	Visual inspection and functional testing	The device does not interfere with the fluid path, therefore does not impact the PFS or needle sterility. Sterility is maintained during the assembly process as indicated in Section P.2.3	Yes

Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Standard Atmosphere conditions according to ISO 11608-1.	ISO 11608-1:2014 Section 10.2	Visual inspections and functionality testing including delivered volume, lockout (n=60)	Delivered volume criteria met: - Mean: 1.05mL - Range: (b) (4) mL - Kact: (b) (4) Needle guard lock-out confirmed for all devices No visual defects.	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Cool Atmosphere conditions according to ISO 11608-1.	ISO 11608-1:2014, Section 10.2	Visual inspections and functionality testing including delivered volume, lockout (n=60)	Delivered volume criteria met: - Mean: 1.06mL - Range: (b) (4) mL - Kact: (b) (4) Needle guard lock-out confirmed for all devices No visual defects	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Warm Atmosphere conditions according to ISO 11608-1.	ISO 11608-1:2014, Section 10.2	Visual inspections and functionality testing including delivered volume, lockout (n=60)	Delivered volume criteria met: - Mean: 1.05mL - Range: (b) (4) mL - Kact: (b) (4) Needle guard lock-out confirmed for all devices No visual defects	Yes

Design Requirement	Reference to ISO Standard	Method of Verification	Design Feature/Results	Conformance with Requirement
The Safety Syringe shall be designed to avoid unintended activation of the safety mechanism.	ISO11608-5:2014 Section 4.1	Visual inspection	To cause activation of the safety mechanism, a force must be applied to the activation fingers (internal feature of the SSD). This therefore prevents unintended activation. Presence of the activation finger flanges can be confirmed in the supplier component drawings.	Yes
The Safety Syringe should not compromise container (e.g.: DP quality) and/or needle sterility.	ISO11608-5:2014 Section 4.1	Visual inspection and functional testing	The device does not interfere with the fluid path, therefore does not impact the PFS or needle sterility. (b) (4) as indicated in Section P.2.3	Yes

Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Standard Atmosphere conditions according to ISO 11608-1.	ISO 11608-1:2014 Section 10.2	Visual inspections and functionality testing including delivered volume, lockout (n=60)	Delivered volume criteria met: - Mean: 1.05mL - Range: (b) (4) mL - Kact: (b) (4) Needle guard lock-out confirmed for all devices No visual defects.	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Cool Atmosphere conditions according to ISO 11608-1.	ISO 11608-1:2014, Section 10.2	Visual inspections and functionality testing including delivered volume, lockout (n=60)	Delivered volume criteria met: - Mean: 1.06mL - Range: (b) (4) mL - Kact: (b) (4) Needle guard lock-out confirmed for all devices No visual defects	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Warm Atmosphere conditions according to ISO 11608-1.	ISO 11608-1:2014, Section 10.2	Visual inspections and functionality testing including delivered volume, lockout (n=60)	Delivered volume criteria met: - Mean: 1.05mL - Range: (b) (4) mL - Kact: (b) (4) Needle guard lock-out confirmed for all devices No visual defects	Yes

Design Requirement	Reference to ISO Standard	Method of Verification	Design Feature/Results	Conformance with Requirement
Delivery of the drug product through the device and corresponding shear forces applied to the product do not adversely impact	NA	Refer to Section P.2.6	No impact to drug product quality when exposed to normal and increased levels of shear stress during drug delivery. Refer to Section P.2.6.	Yes

Design verification data for the Safety Syringe Device:

Section m3.2.P.2.4 Container Closure Safety Syringe contains a summary of the testing design input requirements are satisfied. The following reports have been provided with this submission:

(b) (4) SSD ISO Verification Test Report
 (b) (4) SSD Functional Test Report
 Functional testing after ASTM shipping simulations
 Functionality Test Report on Aged PPQ

7.3.2. Autoinjector

The autoinjector was reviewed by Jacqueline Gertz, Ph.D. Her full review memo is at the end of this review memo.

Functional Performance Requirements for the Autoinjector

Functional Parameter	Criteria	Basis for Requirement
Cap Removal Force	(b) (4)	Usability / human factors
Injection Actuation Force		Usability / human factors
Needle extension		Clinical input to ensure subcutaneous injection
Delivered volume		Clinical input to ensure full dose delivered (ISO 11608)
Injection (Delivery) Time		Usability / human factors
Audible Click		Usability / human factors
Needle Safe Distance		Safety (ISO 23908)
Needle Guard Override		Safety (ISO 23908)

Autoinjector Design Verification Summary

Design Requirement	Reference to ISO Standard	Method of Verification	Design Feature / Results	Conformance with Requirement
The container holder shall allow visibility of the deliverable volume. The manufacturer shall determine, by risk analysis, if a residual scale is required and how much of the deliverable volume shall be visible. The entire deliverable volume must be visible through the window in any functional state of the device.	ISO 11608-1:2014 (Chapter 5.5a)	Verified by visual inspection that the entire deliverable volume is visible through the window in any functional state of the NIS.	Housing with window	Yes
The device shall be designed in such a way that the user can accurately deliver the entire labelled volume from the container for which they are designed	ISO 11608-1:2014 (Chapter 5.5b),	Verified through visual inspection, as part of dose accuracy testing	Autoinjector with integrated non-replaceable pre-filled syringe. Each syringe holds a single dose, whereby the full amount of the deliverable volume is expelled	Yes

It should be evident by visual means to the users when the device is ready for injection	ISO 11608-1:2014 (Chapter 5.5), ISO 11608-5:2014 (Chapter 4.1)	Attribute Testing - Visual inspection of design during functionality testing	Needle guard and plunger components visible and in starting positions signifying readiness for injection. The plunger position is at the top of the window at the start of injection	Yes
Audible click is emitted at the beginning and end of injection	ISO 11608-1:2014 (Chapter 5.5), ISO 11608-5:2014 (Chapter 4.1)	Functionality Testing - Analyst observing device for click presence	Audible clicks present in all devices tested during functionality testing	Yes

(Continued)

Design Requirement	Reference to ISO Standard	Method of Verification	Design Feature / Results	Conformance with Requirement
The device shall indicate, by visual, audible or tactile means, or any combination of these, that the injection stroke has been completed.	ISO 11608-1:2014 (Chapter 5.5) ISO 11608-5:2014 (Chapter 4.1)	Attribute Testing – Visual and acoustic inspection of design during functionality testing	The injection stroke has been completed f: The end of dose click occurred The yellow plunger is visible through the window, is no longer moving and has filled the viewing window	Yes
Needle guard is automatically locked as device is lifted from injection site – should not lock unless injection stroke has been	ISO 11608-5:2014 (Chapter 4.3.6 and 4.3.7)	Functionality Testing	Needle guard automatically shields needle and locks on all devices tested during functionality testing	Yes
The device shall not be able to be reset following injection	ISO 11608-5 (Chapter 4.3.6)	Verified by design	Needle guard automatically shields needle and locks on all devices	Yes
All materials on the external surface of device and potentially contacting user shall meet biocompatibility requirements set forth by ISO 10993	ISO 10993-1:2009	Biocompatibility testing	All patient contact materials demonstrated biocompatibility. Refer to Section 1.4.3	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Standard Atmosphere conditions according to ISO 11608-1	ISO 11608-1:2014, Section 10.2	Functionality Testing including delivered volume (n=60) and lockout	Delivered volume criteria met: Range: (b) (4) mL, k= (b) (4) Cover sleeve lock-out confirmed for all devices	Yes

Table 3 Autoinjector Design Verification Summary

Design Requirement	Reference to ISO Standard	Method of Verification	Design Feature / Results	Conformance with Requirement
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Cool Atmosphere	ISO 11608-1:2014, Section 10.2	Functionality Testing including delivered volume (n=60) and lockout	Delivered volume criteria met: Range: (b) (4) mL, k= (b) (4) Cover sleeve lock-out confirmed for all devices	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Warm Atmosphere	ISO 11608-1:2014, Section 10.2	Functionality Testing including delivered volume testing (n=60) and lockout	Delivered volume criteria met: Range: (b) (4) mL, k= (b) (4) Cover sleeve lock-out confirmed for all devices	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Dry Heat conditions according to ISO 11608-1	ISO 11608-1:2014, Section 10.6	Functionality Testing including delivered volume (n=60) and lockout	Delivered volume criteria met: Range: (b) (4) mL, k= (b) (4) Cover sleeve lock-out confirmed for all devices	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Cold Storage conditions according to ISO 11608-1	ISO 11608-1:2014, Section 10.6	Functionality Testing including delivered volume (n=60) and lockout	Delivered volume criteria met: Range: (b) (4) mL, k= (b) (4) Cover sleeve lock-out confirmed for all devices	Yes

(Continued)

Table 3 Autoinjector Design Verification Summary (Continued)

Design Requirement	Reference to ISO Standard	Method of Verification	Design Feature / Results	Conformance with Requirement
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Free Fall conditions according to ISO 11608-1	ISO 11608-1:2014, Section 10.5	Functionality Testing including delivered volume (n=30) and lockout	Delivered volume criteria met: Range: (b) (4) mL, k= (b) (4) Cover sleeve lock-out confirmed for all devices	Yes
Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Vibration conditions according to ISO 11608-1	ISO 11608-1:2014, Section 10.9	Functionality Testing including delivered volume (n=20) and lockout	Delivered volume criteria met: Range: (b) (4) mL, K= (b) (4) Cover sleeve lock-out confirmed for all devices	Yes

The device shall maintain container closure integrity of the primary drug container during and after storage and transport	Reference ISO 11608-5:2014, Chapter 4.1, "d"	Refer to Section P.2.5	No impact to container closure integrity. Refer to Section P.2.5	Yes
Final assembly process does not impact the drug product quality (including extractables / leachables)	NA	Refer to Section P.2.3	No impact to drug product quality. Refer to Section P.2.3 and the extractables and leachables section in P.2.4	Yes
Delivery of the drug product through the device and corresponding shear forces applied to the product do not adversely impact product quality.	NA	Refer to Section P.2.6	No impact to drug product quality when exposed to normal and increased levels of shear stress during drug delivery. Refer to Section P.2.6.	Yes

Table 4 Autoinjector Design Verification - Functional Performance (Standard Conditions)

Functional Parameter	Criteria	Sample Size	Results Average (Min, Max)
Cap Removal Force	(b) (4)	10	10.05 (b) (4) N
Injection Actuation Force	(b) (4)	10	7.28 (b) (4) N
Needle extension	(b) (4)	10	6.05 (b) (4) mm
Delivered volume	(b) (4)	60	See results in Table 3
Injection (Delivery) Time	(b) (4)	10	8.97 (b) (4) seconds
Audible Click	(b) (4)	60	60/60 passed
Needle Safe Distance	(b) (4)	100	5.57 (b) (4) mm
Needle Cover Override	(b) (4)	100	222.38 (216.05, 226.63) N

Autoinjector Verification testing

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Depth	(b) (4)	Y	Y	N	N	N

Injection Time	(b) (4)	y	y	Y (18, 24 month PMC)	n	n
Dose Accuracy		y	y	y	y	y
Visual/Audible Feedback		Y	Y	N	N	N
Activation Force		y	y	Y (18/24 Month PMC)	N	N
Needle Length	See syringe review					
Needle Gauge						
Needle Connection Type						
Needle Resistance to Bend / Fracture						
Cap Removal Force		y	y	y	y	N
Needle safety override		y	y	y	y	Y

From justification of specifications:

The prefilled syringe is assembled into two device formats, an autoinjector and a safety syringe device. Release of the DP as a combination product (biologic and device) includes testing of product characteristics at their relevant points in the manufacturing process. The release testing for product quality attributes will be performed on the prefilled syringe alone. The release testing performed on the final assembled devices will be limited to device functionality testing to ensure that the final assembly process (device components with the drug-filled prefilled syringe) was properly performed. In order to confirm that the PFS is representative of the AI and SSD, release and stability testing of all formats (PFS, AI, and SSD) has been performed for (b) (4) batches of PFS and their corresponding AI/SSD batches, and the results are provided in P.5.4 Batch Analysis and P.8.3 Stability Data. Results for purity by SEC, CGE and cIEF; potency by SPR and IL-5 neutralisation; concentration by variable pathlength UV/VIS spectrometry; osmolality, appearance, pH and particulate matter are comparable across all formats and all batches.

The DP specification includes the methods shown in Table 2. Release of the prefilled syringe will be a prerequisite to release the assembled device.

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/s/

JI HYUN LAROSE
06/06/2019 03:19:09 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 9, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761122
Product Name and Strength:	Nucala (mepolizumab) Injection 100 mg/mL
Applicant/Sponsor Name:	GlaxoSmithKline, LLC
FDA Received Date:	April 18, 2019
OSE RCM #:	2018-1718-1
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container label and carton labeling for Nucala (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to labeling comments sent to the Sponsor from the Office of Biotechnology Products (OBP).^a

2 CONCLUSION

The Sponsor submitted revised container label and carton labeling received on April 18, 2019 for Nucala. We have no additional recommendations at this time.

^ahttps://darrrts.fda.gov//darrrts/faces/ViewDocument?documentId=090140af804eb798&_afRedirect=3344173827176794

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

PATIENT LABELING REVIEW

Date: April 15, 2019

To: Sally Seymour, MD
Acting Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

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

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

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

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

Drug Name (established name): NUCALA (mepolizumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761122

Applicant: GlaxoSmithKline LLC

1 INTRODUCTION

On August 7, 2018, GlaxoSmithKline submitted for the Agency's review an original Biologics License Application (BLA) 761122 for their product NUCALA (mepolizumab) injection, for subcutaneous use to be administered subcutaneously (SC) via Autoinjector (AI) or a Safety Syringe Device (SSD) pursuant to Section 351(a) of the Public Health Service Act. The liquid mepolizumab and the devices will allow for administration by the patient or caregiver outside of the healthcare setting. The currently approved product, NUCALA (mepolizumab) BLA 125526 is supplied as a lyophilized powder that requires reconstitution before being administered subcutaneously only in a health care setting. NUCALA (mepolizumab) is indicated for severe asthma and eosinophilic granulomatosis with polyangiitis (EGPA).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DARP) on August 31, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFUs) for NUCALA (mepolizumab) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed in DARRTS on March 13, 2019.

2 MATERIAL REVIEWED

- Draft NUCALA (mepolizumab) PPI and IFUs received on August 7, 2018, revised by the Review Division throughout the review cycle, received by DMPP and OPDP on April 2, 2019.
- Draft NUCALA (mepolizumab) Prescribing Information (PI) received on August 7, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 2, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFUs we:

- have simplified wording and clarified concepts where possible

- ensured that the PPI and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFUs meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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

Memorandum

Date: April 11, 2019

To: Xu Wang, Clinical Reviewer
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Ji LaRose, Regulatory Project Manager, DPARP

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

CC: Kathleen Klemm, Team Leader, OPDP

Subject: OPDP Labeling Comments for NUCALA (mepolizumab) injection, for subcutaneous use

BLA: 761122

In response to DPARP's consult request dated August 31, 2018, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labels for the original BLA submission for NUCALA (mepolizumab) injection, for subcutaneous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on April 1, 2019, and are provided below.

PPI and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labels received by electronic mail from DPARP on April 1, 2019, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

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HUMAN FACTORS RESULTS AND LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	March 13, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761122
Product Name and Strength:	(mepolizumab) Injection 100 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GlaxoSmithKline, LLC
FDA Received Date:	August 7, 2018
OSE RCM #:	2018-1731 & 2018-1718
DMEPA Safety Evaluators:	Matthew Barlow, RN, BSN Lissa C. Owens, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD
Associate Director of Human Factors:	QuynhNhu Nguyen, M.S.

1 REASON FOR REVIEW

This review is in response to DPARP's request for DMEPA to evaluate the submitted Human Factors (HF) validation study results submitted by the Applicant on August 7, 2018. The HF study results were submitted under BLA 761122. Additionally, DPARP requested that we review the proposed prescribing information (PI), instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

The Applicant submitted HF validation study results for the autoinjector (AI) and prefilled syringe (PFS) presentations of the proposed product. Additionally, DMEPA sent out an Information Request (IR) on November 19, 2018, to clarify if the same participants were used in the HF study for both the AI and PFS. We also requested further information regarding an observed error in the HF study results with the AI. The Applicant responded to the IR on November 26, 2018, clarifying that different participants were used in the HF study for the PFS and the AI. The Applicant provided information regarding the observed use error in the HF study for the AI.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the HF validation study results, PI, IFU, container labels, and carton labeling for the proposed mepolizumab injection is described below.

3.1 ANALYSIS OF HF VALIDATION STUDY RESULTS

Table 2 describes the errors/close calls/use difficulties observed in the HF study, the Applicant's reporting of the results and proposed mitigations, and DMEPA's analyses and recommendations.

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Table 2: Human Factors Validation Study Results for the Autoinjector					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors and Description of Use Errors	Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Administer Full Dose [C]	1 Use Error (b) (6) (COPD, Untrained): lifted AI up prematurely before the second click.	N/A	(b) (6) rushed did not pay as much attention to the second click information as the information for starting the injection. (b) (6) admitted she was anxious, which may have also attributed to him/her rushing through the process.	No mitigation needed, and no residual risk remains. 1 participant rushed and did not fully learn how to use the device during their own self-familiarization. We would conclude that no revision to the IFU is needed.	The potential harm associated with lifting up the AI early is an underdose. We reached out to the Applicant to request further information regarding this observed error. The Applicant was unable to determine why the AI was lifted prematurely, and the participant was able to explain the proper procedure when given the IFU. Additionally, the participant was able to perform the administration correctly on a second injection attempt. Therefore, we have no recommendations at this time.
Knowledge Probe – Warm to Room Temperature [E]	1 Use Error (b) (6) (Adult Asthma,	N/A	(b) (6) answered based on their memory and not what the instructions stated.	No mitigation needed, and no residual risk remains. This would have resulted in a cold injection, that may be uncomfortable	The harm associated with not warming the product to room temperature is an uncomfortable injection.

	Untrained): When asked what to do after removing the device from the refrigerator (b) (6) (Adult Asthma, Untrained) stated to take the device out and do the injection.		This is a low risk event, per the risk analysis, which if done as the participant stated would result in an uncomfortable, though effective, injection.	to the patient but would not represent an ineffective dose. We would conclude that no revision to the IFU is needed.	The subjective feedback indicated that the participant stated that their mindset was on the product and not the temperature aspect. Additionally, the participant felt the instructions were clear as they were. Our review of the root cause analysis, subjective feedback, and the IFU steps related to this observed error did not identify any recommendations at this time.
Reading Comprehension Question – Use within 5 Minutes of Removing Cap [C]	1 Use Error (b) (6) (COPD, Trained): incorrectly read the warning message that says, “Make sure you inject within 5 minutes of removing the clear needle cap” and read the word “within” as “with”, thus stated a wrong answer to the reading	N/A	(b) (6) read the word “within” as “with” which lead to the incorrect interpretation. (b) (6) did not make this mistake during the unaided trial as (b) (6) Injected immediately after removing the needle cap.	No mitigation needed, and no residual risk remains. Instructions cannot prevent a user from reading a word incorrectly.	The harm associated with not administering the injection within 5 minutes of removing the cap is potential reduced efficacy. The subjective feedback indicated that the participant misinterpreted the word “within” for “with” and answered this question by saying they would remove the cap and wait 5 minutes. We note in the observation notes, the participant read the word “within” correctly when reading the passage out loud but misinterpreted it when providing a response.

	comprehension question despite having injected right away during their unaided injection attempt.				Additionally, the participant administered the injection within 5 minutes of removing the cap during the simulation injection trial. DMEPA reviewed the root cause analysis, subjective feedback, and objective/observation notes. Our review of the root cause analysis, subjective feedback, and the IFU steps related to this observed error did not identify any recommendations at this time.
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Table 3: Human Factors Validation Study Results for the Pre-Filled Syringe					
Tasks (include C for critical and E for essential)	Number of Failures/Use Errors and Description of Use Errors	Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Knowledge Probe - Identify how to get a comfortable injection (Correct Answer: Wait	1 Use Error (b) (6) (Adult Asthma, Untrained): was unable to find	N/A	(b) (6) admitted that s/he was looking only at the pictures and did not find this information because of it.	No mitigation needed, and no residual risk remains. This was a single, low-risk event with no patterns. The participant stated in his/her failure debrief that the instructions clearly	The harm associated with not waiting 30 minutes would be an uncomfortable injection. Our review of the root cause analysis, subjective feedback, and the IFU steps related to this observed error did not

30 minutes) [E]	how to get a comfortable injection after taking the device out of the refrigerator. The moderator then pointed out to P38 what the correct answer was from the IFU. After reviewing the IFU, P38 was able to answer that you should wait 30 minutes to get a comfortable injection.			communicate this information and s/he did not notice it. The participant offered no suggestions for improving the instructions. We would conclude that no revision to the IFU is needed.	identify any recommendations at this time.
Reading Comprehension – Inspecting Drug Passage (Correct Answer: The drug should be clear and colorless to slightly yellow with 1 or more air bubbles) [E]	1 Failure (b) (6) (Caregiver, Untrained): identified yellow drug as bad drug.	N/A	When asked about this, (b) (6) stated that yellow drug was always bad when s/he was trained as a medical technician.	No mitigation needed, and no residual risk remains. (b) (6) stated in her failure debrief that his/her past experiences as a Medtech influenced their answer rather than the content in the IFU. We would conclude that no revision to the IFU is needed.	The harm associated with not inspecting drug is reduced efficacy of medication. We note this participant incorrectly answered due to past clinical experience. Our review of the root cause analysis, subjective feedback, and the IFU steps related to this observed error did not identify any recommendations at this time.

Peeling open syringe tray [E]	N/A	1 Use Difficulty (b) (6) (COPD, Untrained): was unable to peel off the plastic seal from the syringe tray because s/he did not notice a flap from which to peel from. (b) (6) was able to successfully peel open the tray once she saw the flap in the one corner.	(b) (6) did not notice a flap on the tray from which to peel from.	No mitigation needed, and no residual risk remains. No harm would have resulted to the patient. There would have been a small delay in dosing as the user would ask for help from someone else or use scissors to open the package. We would conclude that no revision to the IFU is needed.	The harm associated with not being able to open tray would be a delay in dose. The subjective feedback indicated that the participant was initially unable to find the flap on the tray; however, the participant was able to open the tray once the flap was located. Our review of the root cause analysis, subjective feedback, and the IFU steps related to this observed error did not identify any recommendations at this time.
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3.2 LABELS AND LABELING

In addition to the Human Factors validation study results, we evaluated the proposed labels and labeling for Nucala. Our evaluation of the proposed Nucala prescribing information (PI), instructions for use (IFU), container labels and carton labeling did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

We find the Human Factors validation study results for the pre-filled syringe and autoinjector acceptable and we do not have any recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Nucala received on August 7, 2018 from GlaxoSmithKline, LLC.

Table 4. Relevant Product Information for Nucala	
Initial Approval Date	N/A for BLA 761122 (approved November 4, 2015 under BLA 125526)
Active Ingredient	mepolizumab
Indication	- Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype. - The treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).
Route of Administration	Subcutaneous
Dosage Form	for injection: lyophilized powder in a single-dose vial for reconstitution Injection: single-dose, prefilled autoinjector or single dose prefilled syringe
Strength	100 mg/mL
Dose and Frequency	- Asthma: 100 mg administered subcutaneously once every 4 weeks. - EGPA: 300 mg as 3 separate 100-mg injections administered subcutaneously once every 4 weeks.

How Supplied	• single-dose vials in cartons of 1 • single-dose, prefilled autoinjector with attached 29-gauge, half-inch needle in cartons of 1 • single-dose, prefilled glass syringe with attached 29-gauge, half-inch needle in cartons of 1
Storage	• Store vials below 77°F (25°C). Do not freeze. Store in the original carton to protect from light • Refrigerate prefilled autoinjectors and prefilled syringes at 36°F to 46°F (2°C to 8°C). Keep the product in the original carton to protect from light. Do not freeze • If necessary, an unopened carton can be stored outside the refrigerator at up to 86°F (30°C) for up to 7 days. Discard if left out of the refrigerator for more than 7 days
Container Closure	• The safety syringe device utilizes commercially available components specifically designed for prefilled syringes. These components include a needle guard, which is a passive anti-needle stick device possessing 510k clearance • (b) (4) the needle is covered by the cover sleeve at all times. After the dose is delivered, the cover sleeve locks into position over the needle, preventing re-use and needle stick injuries

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 1, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Nucala. Our search identified one previous review^a, and we confirmed that our previous recommendations were implemented.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design & Results

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APPENDIX D. ISMP NEWSLETTERS—N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)—N/A

APPENDIX F.—N/A

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^a Owens, L. Human Factors Validation Protocol and Label and Labeling Review for Nucala (IND 006971). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 10. RCM No.: 2017-974 and 2017-975.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Nucala labels and labeling submitted by GlaxoSmithKline, LLC.

- Container label received on August 7, 2018
- Carton labeling received on August 7, 2018
- Professional Sample Carton Labeling received on August 7, 2018
- Professional Sample Container Label received on August 7, 2018
- Instructions for Use (Image not shown) received on August 7, 2018
- Prescribing Information (Image not shown) received on August 7, 2018

G.2 Label and Labeling Images

Container labels

Autoinjector

Syringe

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

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