CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761043Orig1s000

OTHER REVIEW(S)

7/13/17

U.S. FOOD & DRUG ADMINISTRATION

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

LABELS AND LABELING REVIEW

Date:	July 13, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Sean Fitzsimmons, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research I
Application:	BLA 761043
Product:	Benlysta (b) (4) (belimumab)
Applicant:	Human Genome Sciences, Inc.
Submission Date(s):	September 22, 2016, February 15, 2017, June 23, 2017, and July 12, 2017

I) RECOMMENDATION

The labels and labeling for Benlysta (b) (4) (belimumab) Injection 200 mg/mL single-dose autoinjector or prefilled syringe for subcutaneous use submitted on June 23, 2017 (container label and carton labeling) and July 12, 2017 (prescribing information/medication guide) are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant submitted BLA 761043 Benlysta (b) (4) (belimumab) injection on September 22, 2016, which provides for new dosage form, route of administration, strength, and dosing regimen of belimumab.

Benlysta (belimumab) for injection was approved in year 2011 (BLA 125370), as 120 mg and 400 mg lyophilized powder in single-dose vials for intravenous infusion after reconstitution and further dilution administered as weight based dosing of 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. These two dosage forms will share a PI.

Table 1: Proposed Product Characteristics of Benlysta (b) (4) (belimumab).

Proprietary Name:	Benlysta (b) (4)
Nonproprietary Name:	belimumab
Dosage Form:	Injection
Strength and Container-Closure:	200 mg/mL prefilled autoinjector or prefilled syringe (safety syringe)
Route of Administration:	subcutaneous

Storage and Handling:	Store autoinjectors and prefilled syringes refrigerated between 2°C to 8°C (36°F to 46°F) and protected from light. Keep the product in the original carton to protect from light until the time of use. Do not freeze. Do not shake. Avoid exposure to heat. Do not use if left out at room temperature for more than 12 hours.
Indication:	for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy
Dose and Frequency:	200 mg once weekly given as a subcutaneous injection in the abdomen or thigh. Dosing is not based on weight

III) MATERIALS REVIEWED

We considered the materials listed in Table 2 for this review.

Table 2: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B
Relevant Code of Federal Regulations and CDER Labeling Best Practices	C
Acceptable Labels and Labeling	D

n/a = not applicable for this review

IV) DISCUSSION

The proposed labels were evaluated for compliance to the applicable code of federal regulations and CDER Labeling Best Practices (see Appendix C).

V) CONCLUSION

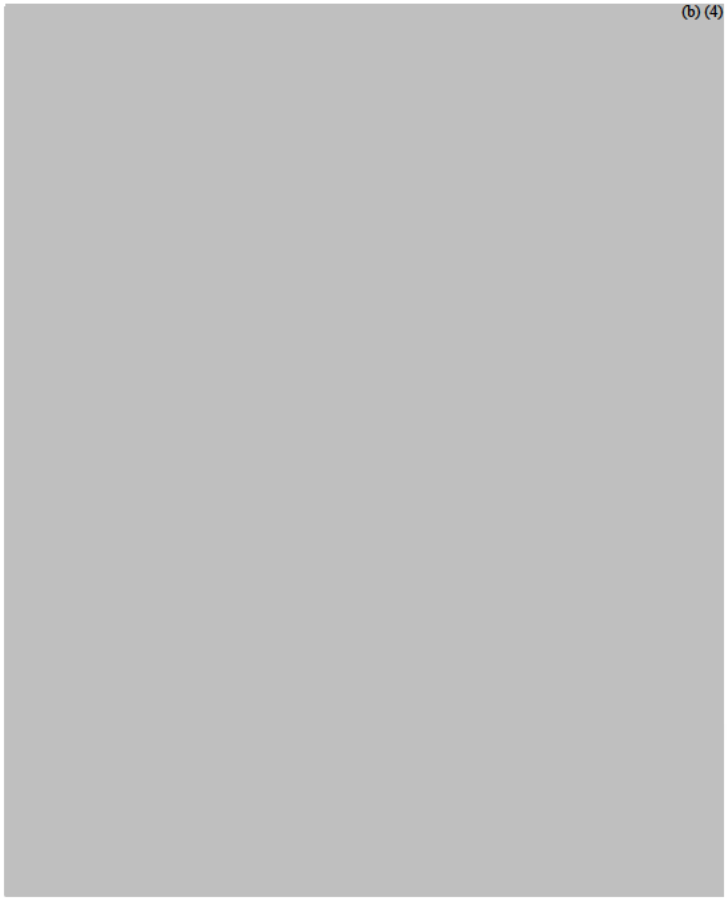
The prescribing information, medication guide, instructions for use, container labels, and carton labeling for Benlysta (b)(4) (belimumab) Injection 200 mg/mL single-dose prefilled autoinjector or prefilled syringe for subcutaneous use were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57; 21 CFR 201.100 and United States Pharmacopeia (USP). The labels and labeling submitted on June 23, 2017 (container label and carton labeling) and July 12, 2017 (prescribing information/medication guide) are acceptable from a quality perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted February 15, 2017)
- Medication Guide submitted February 15, 2017
- Instructions for Use (submitted February 15, 2017 - \\cdsesub1\evsprod\bla761043\0008\m1\us\114-labeling\1141-draft\draft-200mg-ifu-ai.doc and \\cdsesub1\evsprod\bla761043\0008\m1\us\114-labeling\1141-draft\draft-200mg-ifu-pfs.doc)

Container Labels (submitted February 15, 2017)



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

Appendix B: Other

Appendix C: Applicant Code of Federal Regulations and CDER Best Labeling Practices

Table 3: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Auto injector container label

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Proper Name 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10			x	We consider this a partial label. See assessment below
Manufacturer name, address, and license number 21 CFR 610.60			x	We consider this a partial label. See assessment below
Lot number or other lot identification 21 CFR 610.60 21 CFR 201.18 21 CFR 201.100			x	We consider this a partial label. See assessment below
Expiration date 21 CFR 610.60 21 CFR 201.17			x	We consider this a partial label. See assessment below
Multiple dose containers (recommended individual dose)			x	Single-dose prefilled autoinjector

[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 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.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.60				
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100			x	We consider this a partial label
Medication Guide 21 CFR 610.60 21 CFR 208.24			x	We consider this a partial label and the MG statement will be placed on the carton labeling per 21 CFR 610.60(a)(7).
No Package for container 21 CFR 610.60			x	
Partial label 21 CFR 610.60 21 CFR 201.10		x		If space permits, include the license number below the manufacturer name on the principal display panel of the autoinjector container label. *The applicant's revision is acceptable* See DMEPA's Label, Labeling And Human Factors Results Review regarding approving the proper name as designated without a suffix [and intend to work with the applicant post-approval to implement a proper name consistent with the principles outlined in the guidance].[5]
No container label 21 CFR 610.60			x	
Visual inspection 21 CFR 610.60		x		Confirm that there is sufficient area on the container to allow for visual inspection of the contents when the label is affixed to the container per 21 CFR 610.60 (e). *The applicant's response is acceptable*
NDC numbers 21 CFR 201.2 21 CFR 207.35	x			
Route of administration 21 CFR 201.5 21 CFR 201.100	x			

[5] Patel M. Label, Labeling and Human Factors Results Review for Benlysta (b) (4) (belimumab) injection (BLA 761043). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 May 31.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Preparation instructions 21 CFR 201.5	x			
Package type term 21 CFR 201.5	x			If space permits, add the package type term to the back panel of the autoinjector container label as follows: "Single-dose prefilled autoinjector" *The applicant's revision is acceptable*
Drugs Misleading statements 21 CFR 201.6			x	
Strength 21 CFR 201.10 21 CFR 201.100		x		The strength per single mL should be expressed as mg/mL, (b) (4) Revise the strength so that it is expressed as mg/mL per USP General Chapters <7>. Revise from (b) (4) to read: "200 mg/mL". *The applicant's revision is acceptable*
Drugs Prominence of required label statements 21 CFR 201.15	x			
Bar code label requirements 21 CFR 201.25 21CFR 610.67	x			
Net quantity 21 CFR 201.51	x			We consider this a partial label however See recommendation for package type term above
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	x			We consider this a partial label and this information must appear on the carton, PI, and IFU (if applicable).
Inactive ingredients 21 CFR 201.100	x			We consider this a partial label and this information must appear on the carton, PI, and IFU (if applicable).
Storage requirements	x			

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Dispensing container 21 CFR 201.100			x	

Prefilled syringe container label

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
Proper Name 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10			x	We consider this a partial label. See assessment below
Manufacturer name, address, and license number 21 CFR 610.60			x	We consider this a partial label. See assessment below
Lot number or other lot identification 21 CFR 610.60 21 CFR 201.18 21 CFR 201.100			x	We consider this a partial label. See assessment below
Expiration date 21 CFR 610.60 21 CFR 201.17			x	We consider this a partial label. See assessment below
Multiple dose containers (recommended individual dose) 21 CFR 610.60			x	single-dose prefilled syringe
Statement: "Rx only" 21 CFR 610.60 21 CFR 201.100			x	We consider this a partial label. See assessment below
Medication Guide 21 CFR 610.60			x	We consider this a partial label and the MG statement will be placed on the carton labeling per 21 CFR

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
21 CFR 208.24				610.60(a)(7).
No Package for container 21 CFR 610.60			x	
Partial label 21 CFR 610.60 21 CFR 201.10		x		We consider this a partial label. Add the required manufacturer name "Human Genome Sciences, Inc." per 21 CFR 610.60(c). Consider removing the non-required NDC number to make space for required information such as the manufacturer name. *The applicant's revision is acceptable*
No container label 21 CFR 610.60			x	
Visual inspection 21 CFR 610.60		x		Confirm there is sufficient area on the container when the label is affixed to the container to allow for visual area of inspection of the contents per 21 CFR 610.60 (e). *The applicant's response is acceptable*
NDC numbers 21 CFR 201.2 21 CFR 207.35			x	We consider this a partial label. Not required for partial labels per 21 CFR 610.60(c).
Route of administration 21 CFR 201.5 21 CFR 201.100			x	We consider this a partial label. This information must appear on the carton, PI, and IFU (if applicable).
Preparation instructions 21 CFR 201.5			x	We consider this a partial label.
Package type term 21 CFR 201.5			x	We consider this a partial label.
Drugs Misleading statements 21 CFR 201.6	x			
Strength 21 CFR 201.10 21CFR 201.100		x		The strength per single mL should be expressed as mg/mL, (b) (4). Revise the strength so that it is expressed as mg/mL per USP General Chapters <7>. Revise from (b) (4)" to read: "200 mg/mL" and increase the prominence.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
				The applicant's revision is acceptable
Drugs Prominence of required label statements 21 CFR 201.15		x		See partial label assessment above regarding NDC number, which is non-required information.
Bar code label requirements 21 CFR 201.25 21CFR 610.67			x	We consider this a partial label with insufficient space to permit a barcode on the prefilled syringe. The product must remain in the carton until use and the barcode will appear on the carton label.
Net quantity 21 CFR 201.51			x	We consider this a partial label.
Usual dosage statement 21 CFR 201.55 21 CFR 201.100			x	We consider this a partial label. This information must appear on the carton, PI, and IFU (if applicable).
Inactive ingredients 21 CFR 201.100			x	We consider this a partial label. This information must appear on the carton, PI, and IFU (if applicable).
Storage requirements			x	We consider this a partial label.
Dispensing container 21 CFR 201.100			x	

Package Label[6] Evaluation

Auto injector Carton Labeling (trade box of 4, trade box of 1 replacement, and sample)

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Proper name 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10	x			

[6] 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.

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Manufacturer name, address, and license number 21CFR 610.61	x			
Lot number or other lot identification 21 CFR 610.61	x			
Expiration date 21 CFR 610.61 21 CFR 201.17	x			
Preservative 21 CFR 610.61		x		If no preservative, ensure "No preservative" appears on the side panel per 21 CFR 610.61 (e). *The applicant's revision is acceptable*
Number of containers 21 CFR 610.61	x			
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100		x		The strength per single mL should be expressed as mg/mL, (b) (4).. Revise the strength so that it is expressed as mg/mL per USP General Chapters <7>. Revise from (b) (4) to read: "200 mg/mL". Relocate to the strength statement to appear beneath the dosage form on all panels as follows: Benlysta (b) (4) (belimumab) Injection 200 mg/mL *The applicant's revision is acceptable*
Storage temperature 21 CFR 610.61		x		Revise the storage information to read as follows to include important storage information for the end user: **"Store refrigerated at 2°C to 8°C (36°F to 46°F)** in the original carton until time of use to PROTECT FROM LIGHT. DO NOT FREEZE. DO NOT SHAKE. (b) (4)

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				Benlysta (b) (4) may be stored (b) (4) for up to 12 hours in the original carton. Do not use and do not place back in the refrigerator if left out (b) (4) for more than 12 hours." *Applicant revised storage conditions to "BENLYSTA may be stored outside of the refrigerator up to 86°F (30°C) for up to 12 hours in the original container. Do not use and do not place back in refrigerator if left out for more than 12 hours.". The applicant's revision is acceptable.*
Handling: "Shake Well", "Do not Freeze" or equivalent 21 CFR 610.61	x			
Multiple dose containers (recommended individual dose) 21 CFR 610.61			x	single-dose
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	x			
Known sensitizing substances 21 CFR 610.61			x	
Antibiotics added during manufacturing 21 CFR 610.61			x	
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Adjuvant, if present 21 CFR 610.61			x	
Source of the product 21 CFR 610.61			x	
Identity of each microorganism used in manufacturing 21 CFR 610.61	x			Listing in the PI in section 11 DESCRIPTION is sufficient
Minimum potency of product 21 CFR 610.61		x		Add "No U.S. standard of potency" to the side panel per 21 CFR 610.61 (r) *The applicant's revision is acceptable*
Rx only 21CFR 610.61 21 CFR 201.100	x			
Divided manufacturing 21 CFR 610.63			x	
Distributor 21 CFR 610.64			x	
Bar code 21 CFR 610.67 21 CFR 201.25	x			
NDC numbers 21 CFR 201.2 21 CFR 207.35	x			
Preparation instructions 21 CFR 201.5	x			
Package type term 21 CFR 201.5		x		Revise the package type term on the principal display panel from "Single-Dose Autoinjector" to read as follows: "Single-Dose 1 mL Prefilled Autoinjector" to include the net quantity (1 mL) and to clarify that the autoinjector is prefilled. The net quantity should appear on the PDP per Draft Guidance: Safety Considerations for Container Labels and Carton

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				Labeling Design to Minimize Medication Errors, April 2013 *The applicant's revision is acceptable* Revise the Contents statement on the side panel to add the package type term to read as follows: "CONTENTS: Each single-dose 1 mL prefilled autoinjector delivers 200 mg belimumab, L-arginine hydrochloride (5.3 mg), L-histidine (0.65 mg), L-histidine monohydrochloride (1.2 mg), polysorbate 80 (0.1 mg), and sodium chloride (6.7 mg)". *The applicant's revision is acceptable*
Drugs Misleading statements 21 CFR 201.6	x			
Drugs Prominence of required label statements 21 CFR 201.15	x			
Net quantity 21 CFR 201.51	x			
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	x			
Dispensing container 21 CFR 201.100			x	
Medication Guide 21 CFR 610.60 21 CFR 208.24	x			

Prefilled Syringe Carton Labeling (trade box of 4, trade box of 1 replacement, and sample)

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
Proper name 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10	x			
Manufacturer name, address, and license number 21CFR 610.61	x			
Lot number or other lot identification 21 CFR 610.61	x			
Expiration date 21 CFR 610.61 21 CFR 201.17	x			
Preservative 21 CFR 610.61		x		If no preservative, ensure "No preservative" appears on the labeling per 21 CFR 610.61 (e). *The applicant's revision is acceptable*
Number of containers 21 CFR 610.61	x			
Strength/volume 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100		x		The strength per single mL should be expressed as mg/mL, (b) (4). Revise the strength so that it is expressed as mg/mL per USP General Chapters <7>. Revise from (b) (4) to read: "200 mg/mL". Relocate to appear beneath the dosage form on all panels as follows: Benlysta (b) (4) (belimumab) Injection 200 mg/mL *The applicant's revision is acceptable*
Storage temperature				Revise the storage information to read as follows to include important storage information for the end

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.61				user: **"Store refrigerated at 2°C to 8°C (36°F to 46°F)** in the original carton until time of use to PROTECT FROM LIGHT. DO NOT FREEZE. DO NOT SHAKE. (b) (4) Benlysta (b) (4) may be stored (b) (4) for up to 12 hours in the original carton. Do not use and do not place back in the refrigerator if left out (b) (4) for more than 12 hours." *Applicant revised storage conditions to "BENLYSTA may be stored outside of the refrigerator up to 86°F (30°C) for up to 12 hours in the original container. Do not use and do not place back in refrigerator if left out for more than 12 hours.". The applicant's revision is acceptable.*
Handling: "Shake Well", "Do not Freeze" or equivalent 21 CFR 610.61	x			
Multiple dose containers (recommended individual dose) 21 CFR 610.61			x	single dose
Route of administration 21CFR 610.61 21 CFR 201.5 21 CFR 201.100	x			
Known sensitizing substances 21CFR 610.61			x	
Antibiotics added during			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
manufacturing 21 CFR 610.61				
Inactive ingredients 21 CFR 610.61 21 CFR 201.100	x			
Adjuvant, if present 21 CFR 610.61			x	
Source of the product 21 CFR 610.61			x	
Identity of each microorganism used in manufacturing 21 CFR 610.61	x			
Minimum potency of product 21 CFR 610.61		x		Add "No U.S. standard of potency" to the side panel per 21CFR 610.61 (r) *The applicant's revision is acceptable*
Rx only 21CFR 610.61 21 CFR 201.100	x			
Divided manufacturing 21 CFR 610.63			x	
Distributor 21 CFR 610.64			x	
Bar code 21 CFR 610.67 21 CFR 201.25	x			
NDC numbers 21 CFR 201.2 21 CFR 207.35	x			
Preparation instructions 21 CFR 201.5	x			
Package type term		x		Revise the package type term on the principal display panel from "x Single-Dose Prefilled Syringes" to read

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.5				as follows: "x Single-Dose 1 mL Prefilled Syringes" to include the net quantity (1 mL) and to clarify that the PFS is prefilled. The net quantity should appear on the PDP per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013. *The applicant's revision is acceptable* Revise the Contents statement on the side panel to add the package type term to read as follows: "CONTENTS: Each single-dose 1 mL prefilled syringe delivers 200 mg belimumab, L-arginine hydrochloride (5.3 mg), L-histidine (0.65 mg), L-histidine monohydrochloride (1.2 mg), polysorbate 80 (0.1 mg), and sodium chloride (6.7 mg)". *The applicant's revision is acceptable*
Drugs Misleading statements 21 CFR 201.6	x			
Drugs Prominence of required label statements 21 CFR 201.15	x			
Net quantity 21 CFR 201.51	x			
Usual dosage statement 21 CFR 201.55 21 CFR 201.100	x			
Dispensing container 21 CFR 201.100			x	
Medication Guide 21 CFR 610.60 21 CFR 208.24	x			

Prescribing Information and Patient Labeling Evaluation

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
PRESCRIBING INFORMATION				
Highlights of prescribing information				
PRODUCT TITLE 21 CFR 201.57(a)(2)	x			
DOSAGE AND ADMINISTRATION 21 CFR 201.57(a)(7)	x			
DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(a)(8)		x		Per 21 CFR 201.57(a)(8), remove (b) (4) (b) (4) as it is not required information for this section. However, the strength should be expressed as mg/mL per USP Chapter <7>. Added subsections "intravenous Infusion and Subcutaneous Injection" Revise from (b) (4) To read: "Intravenous Infusion For injection: 120 mg or 400 mg lyophilized powder in single-dose vials for reconstitution and dilution prior to intravenous infusion. Subcutaneous Injection Injection: 200 mg/mL single-dose prefilled autoinjector or a single-dose prefilled syringe" *Applicant accepted revisions*
Full Prescribing Information				
2 DOSAGE AND ADMINISTRATION 21 CFR 201.57(c)(3)	x			
3 DOSAGE FORMS AND STRENGTHS 21 CFR 201.57(c)(4)		x		Per 21 CFR 201.57(c)(4), we removed (b) (4) (b) (4) as these are not required information for this section. However, the strength should be expressed as mg/mL per USP Chapter <7>. We added identifying characteristics. Revise from (b) (4)

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				[redacted] (b) (4) To read "Intravenous Infusion For injection: 120 mg or 400 mg lyophilized powder in single-dose vials for reconstitution and dilution prior to intravenous infusion. Subcutaneous Injection Injection: 200 mg/mL as a clear to opalescent, and colorless to pale yellow solution in a single-dose prefilled autoinjector or a single-dose prefilled syringe" *Applicant accepted revisions*
6.2 IMMUNOGENICITY		x		Relocated and revised the language for this standard statement based on our current labeling best practice see draft Guidance for Industry: Labeling for Biosimilar Products) *Applicant accepted revisions*
11 DESCRIPTION 21 CFR 201.57(c)(12)		x		Deleted [redacted] (b) (4) from the first paragraph since this paragraph discussed the drug substance. *Applicant accepted revisions* Added subsections for each dosage form, the proper name, and package type term to the second paragraph. *Applicant accepted revisions* Added cell substrate "murine cell (NS0) expression system" *Applicant accepted revisions*
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)		x		Revised the subsection titles to "for intravenous infusion and for subcutaneous injection, and revised how supplied statement to express the strength as mg/mL per USP Chapter <7> Labeling. We added the identifying characteristics per 21 CFR 201.57(c)(17). We

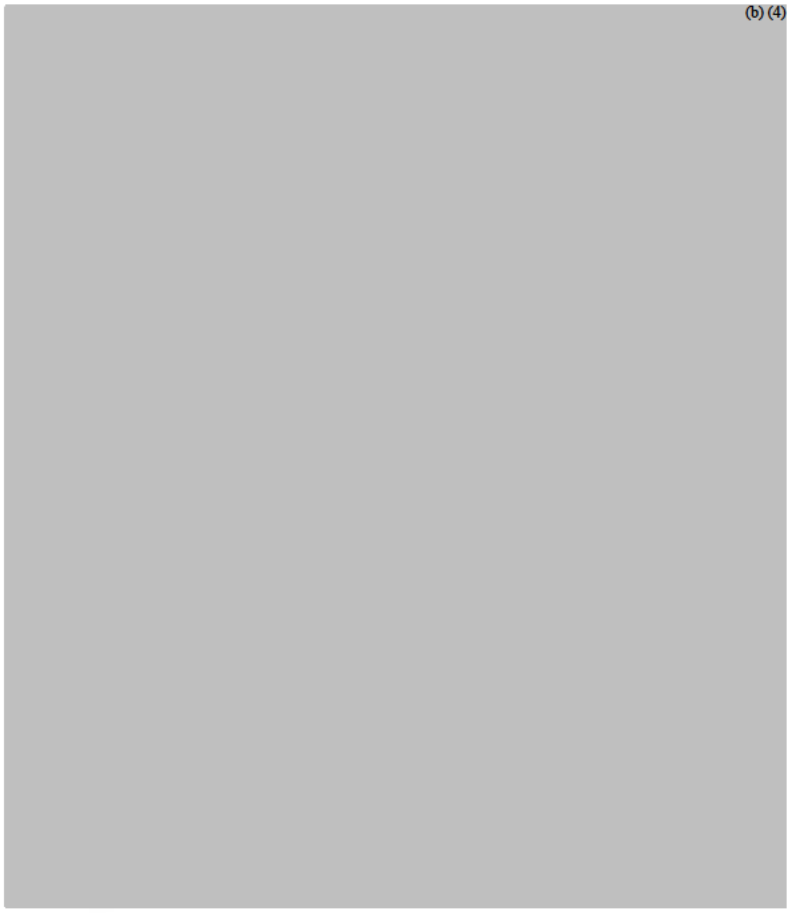
Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				added the deliverable volume per OND best labeling practice. BENLYSTA (b) (4) (belimumab) Injection is a clear to opalescent, and colorless to pale yellow solution for subcutaneous use. Each single-dose pre-filled auto-injector or a single-dose prefilled syringe is designed to deliver 200 mg of belimumab in 1 mL of solution and is supplied as follows: 200 mg/mL single-dose prefilled autoinjector with 27-gauge, half-inch needle attached (NDC 49401-088-01) in a carton of 4 (NDC 49401-088-35) 200 mg/mL single-dose prefilled glass syringe with 27-gauge, half-inch needle attached (NDC 49401-088-42) in a carton of 4 (NDC 49401-088-47) *Applicant's revisions are acceptable*
Manufacturer information 21 CFR 610.61 21 CFR 610.64	x			
MEDICATION GUIDE, INSTRUCTIONS FOR USE, AND PATIENT INFORMATION				
Title (names and dosage form)	x			
Storage and Handling		x		For the Medication guide: OBP Recommends to add "Do not shake. (b) (4) Do not use if left out at room temperature for more than 12 hours." To the How should I store BENLYSTA (b) (4)? section. *Applicant accepted revisions*
Ingredients	x			
Manufacturer Information 21 CFR 610.61, 21 CFR 610.64	x			

APPENDIX D. Acceptable Labels and Labeling

- Prescribing Information/Medication Guide submitted July 12, 2017

Container Labels

(b) (4)



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

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance (OC)

Date:	July 12, 2017
To:	Melinda Bauerlien, CDER/OPRO/DRBPMI/RBPMBI, E-mail: Melinda.Bauerlien@fda.hhs.gov CDER/OPQ/OPF: Juandria.Williams@fda.hhs.gov
From:	Jamie Kamon-Brancazio, REGO/DMQ/OC, CDRH, WO 66, Rm 3427, E-mail: Jamie.Kamon-Brancazio@fda.hhs.gov

Jamie Kamon-brancazio -A

Digitally signed by Jamie Kamon-brancazio -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001568505, cn=Jamie Kamon-brancazio -A
Date: 2017.07.13 11:15:45 -04'00'

Applicant/Licensure:	Glaxo Smith Kline Operations UK Ltd
Submission (Type & Number):	BLA 761043/0
Combination Product Name:	Benlysta (belimumab)
Combination Product Intended Use:	Active, autoantibody-positive systemic lupus erythematosus
ICCR Number:	ICCR2016-00245
ICCR Instruction (ICCR Form):	Consultative Review
Pre-Approval Inspection:	No
Documentation Review (Status):	Complete Adequate
CDRH/OC Recommendation:	Approvable

The Office of Compliance at CDRH received a consult request from CDER to evaluate BLA 761043/0, to review the results of the device constituent manufacturing inspection and to review the 21 CFR 820 requirements of the combination product.

Site inspection evaluation

A drug inspection was performed at the Glaxo Smith Kline facility in County Durham, United Kingdom. The pre-approval inspection was conducted to support the approval of BLA 761043, Benlysta (belimumab) drug product manufacturing. This inspection covered six systems.

A four item 483 was issued to the firm at the conclusion of the inspection including: 1) Equipment used in the manufacturing process is not adequately maintained; 2) Corrective and preventative action has not been taken in a timely manner; 3) Testing for GMP utilities is not adequate; and 4) The reference standard used in drug product identification testing is not adequately controlled. The inspection covered the following systems:

CDRH Office of Compliance Recommendation

The Office of Compliance at CDRH has completed the evaluation of application BLA 761043/0 and has the following recommendations:

CDRH recommends approval for BLA 761043/0 based on the status of the recent inspection at Glaxo Smith Kline facility in County Durham, United Kingdom. This inspection was classified VAI.

The desk review of the responses provide for compliance with the Medical Device Regulations showed no deficiencies, CDRH would recommend a review of the final validation data collected on the final combination product post-approval.

Crystal Lewis -S

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Date: 2017.07.12 12:27:54 -04'00'

Crystal Lewis

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/s/

JESSICA K LEE
07/13/2017
Signed on behalf of CDRH OC

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

PATIENT LABELING REVIEW

Date:	July 13, 2017
To:	Badrul Chowdhury, MD Director **Division of Pulmonary, Allergy and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, RN, MSHS-PH, BSN Associate Director, Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams MSN, BSN, RN Acting Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, MSN/Ed. 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: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name:	BENLYSTA (belimumab)
Dosage Form and Route:	for injection, for intravenous use injection, for subcutaneous use
Application Type/Number:	BLA 761043
Applicant:	Human Genome Sciences

1 INTRODUCTION

On September 22, 2016, Human Genome Sciences submitted a Biologics License Application (BLA 761043) for a liquid formulation of BENLYSTA (belimumab) for the treatment of patients with systemic lupus erythematosus (SLE). Subsequently, on June 23, 2017, Human Genome Sciences submitted an amendment to the pending application. This amendment is to provide a consolidated, proposed USPI and Medication Guide for both the intravenous (IV) and subcutaneous (SC) formulations of BENLYSTA (belimumab), for injection. BENLYSTA (belimumab) injection was originally approved on March 9, 2011 and is indicated for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus who are receiving standard therapy.

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 (DPARP) on November 4, 2016, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for BENLYSTA (belimumab), for injection, for intravenous use and injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft BENLYSTA (belimumab), for injection MG and IFU received on June 23, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on July 6, 2017.
- Draft BENLYSTA (belimumab), for injection MG and IFU received on June 23, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on June 26, 2017.
- Draft BENLYSTA (belimumab), for injection Prescribing Information (PI) received on June 23, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on July 6, 2017.
- Draft BENLYSTA (belimumab), for injection Prescribing Information (PI) received on June 23, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on June 26, 2017.

3 REVIEW METHODS

In 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for*

People with Vision Loss. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU 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 MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

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/s/

TWANDA D SCALES
07/13/2017

KYLE SNYDER
07/13/2017

SHARON W WILLIAMS
07/13/2017

LASHAWN M GRIFFITHS
07/13/2017

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

GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM

Date: July 11, 2017

To: Jessica Lee Senior Regulatory Health Project Manager
CDER/OND/ODEII/DPARP

From: LCDR Keith Marin

Through: CDR Alan Stevens, Branch Chief
General Hospital Devices Branch

Subject: Consult for BLA 761043, ICC1600792

Applicant	GlaxoSmithKline (GSK)]
Indication for Use	Treatment of patients with systemic lupus erythematosus (SLE).
Drug / Biologic Constituent	BENLYSTA® (belimumab) for Subcutaneous Injection
Device Constituent	Autoinjector and safety syringe

Recommendation: **Approval**

Based on information reviewed BLA 761061, the sponsor has provided sufficient information for the prefilled syringe and autoinjector. All interactive review questions have been satisfactorily addressed. As a result, CDRH/ODE recommends approval for the BLA for this combination product.

Digital Signature Concurrence Table	
Reviewer	Keith G. Marin -S Digitally signed by Keith G. Marin -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith G. Marin -S, 0.9.2342.19200300.100.1.1=00112503 97 Date: 2017.07.11 14:49:40 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001 89211, cn=Alan M. Stevens -S Date: 2017.07.11 14:56:04 -04'00'

Review Contents

Purpose / Background

The Center for Drug Evaluation and Research (CDER) has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding a review request for BLA 761043. The device constituent of this combination product consists of an autoinjector and pre-filled safety syringe designed to deliver BENLYSTA® (belimumab) for subcutaneous injection. Belimumab (Benlysta) is a recombinant human IgG1 monoclonal antibody that binds and antagonizes the biological activity of soluble B lymphocytes stimulator (BLys) protein, a member of the tumour necrosis factor (TNF) ligand superfamily that promotes the survival of B lymphocytes. High serum BLys levels have been shown to be associated with SLE disease activity [Petri, 2008b] and to increase the risk of clinically meaningful flare over the following year [Petri, 2013]. Given the apparent role of BLyS in autoimmune disease, belimumab was developed for the treatment of patients with systemic lupus erythematosus (SLE).

The original consult request from CDER indicates that, “We request CDRH to review the product device and request CDRH OC to inspect the DP facility.”

The device presentation that is being evaluated within this review is an autoinjector. Device performance will be the focus of this review. Device/drug compatibility will be deferred to CDER.

There is no record of past CDRH interaction related to this combination product.

Reviewer’s Note: Initially it was not clear whether CDER needed a performance review as their consult originally stated they wanted a facilities review. It was clarified to CDER that they needed to submit a separate consult to CDRH/OC to evaluate the manufacturing facilities while ODE evaluate.

Product	Indications for Use
BENLYSTA for subcutaneous injection	Indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

I. Administrative

Documents Reviewed:

Document Title	Document Number	Date -Version	Location
Labeling	1.14 Labeling	09/22/2016	GSR Sequence 0000 / Section 1.14
Specifications	3.2.P.5.1	09/22/2016	GSR Sequence 0000 /

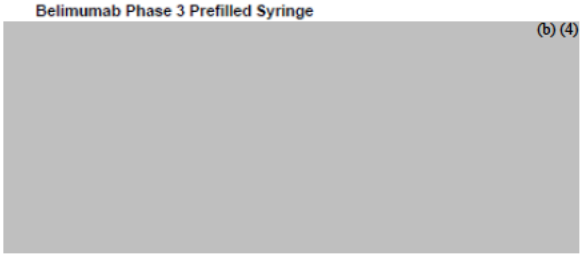
			Section 3.2.P.5.1
Container Closure	3.2.P.7	09/22/2016	GSR Sequence 0000 / Section 3.2.P.7
Stability	3.2.P.8	09/22/2016	GSR Sequence 0000 / Section 3.2.P.8
Summative Human Factors Validation Report	3.2.R	09/22/2016	GSR Sequence 0000 / Section 3.2.R

CDRH Review Team:

Team Member	Role	Deficiencies
LCDR Keith Marin, CDRH/ODE/DAGRID	Lead Reviewer – {Expertise}	#...

II. rmance Requirements

Figure 1 Belimumab Phase 3 Prefilled Syringe



The fo r Closure Document under 3.2.P.7.

Pre-fill

Device Characteristic	Description / Specification
Syringe Barrel Material Type	Glass barrel
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked	1 mL long, (b) (4) USP (b) (4) glass syringe with staked, ½ inch, 27G, (b) (4) needle, preassembled with the rigid needle shield (b) (4)
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self-administration
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	mL
Storage conditions and expiry	storage condition of 2-8°C, protected from light, 36 month shelf life

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.	(b) (4)
	(b) (4)

(b) (4)

Device Characteristic	Description / Specification
Injector Name	Benlysta (belimumab) autoinjector
Delivered volume	Gravimetic method in accordance with ISO 11608-1 (1.0-1.1mL)

Dose accuracy	Device is able to function and meet dose accuracy (delivered volume) requirements when exposed to Standard Atmosphere, cool, warm, dry heat, cold storage, damp heat, cyclic, free fall, and vibration conditions according to ISO 11608-1
Injection Time	Determination of the duration between start and end of product flow using a camera (5-15 seconds)
Injection Site	Abdomen or thighs
Injection tissue and depth of injection	subcutaneous
Audible / visual feedback	Visual indicators (purpose indicator/ (b) (4), (b) (4) (click)
Cap Removal Force	(b) (4)
Activation Force	
Visibility of medication container	Inspection window present
Needle Specifications • Length(s) • Gauge(s) • Connection type ○ ISO 11608-2:2012 ○ Prestaked	27G x ½" (b) (4) needle
Type of Use (e.g. single use, disposable, reusable, other)	Single (b) (4)
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Self-adminsitration
Injection mechanism (e.g., manual piston, spring, gas, etc.)	(b) (4)
Method of actuation	Pressed down onto injection site
Automated Functions	Gold needle guard (b) (4)
Drug Container Type	Pre-filled glass syringe
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	mL
Environments of use	Home use
Storage conditions and expiry	storage condition of 2-8°C, protected from light, 36 month shelf life

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.	(b) (4)
Safety Features • Needle safety	
Material composition of injector	

Reviewer's Note: *Within Sequence 0* (b) (4) (b) (4) (b) (4) *specifications ("In P.5.6 you stat based on release and stability data from M18 and M21 lots, however, an upper limit value of* (b) (4) *was observed in both release and stability samples, with an average* (b) (4) *range of* (b) (4) *An upper limit of* (b) (4) *does not appear to be justified. Please comment."), the sponsor stated that the limit for the maximum* (b) (4) (b) (4) *was based on ensuring that the devices (autoinjector and safety syringe) can be actuated to start delivering the dose, and therefore not primarily on release and stability data from M18 and M21 lots.* (b) (4) (b) (4) *The sponsor has stated that they are amending*

the specifications for the autoinjector based on the current design verification testing and manufacturing data received. The specifications are being changed to the following:

Specification Title	Existing Specification	Revised Specification
Delivery Time	(b) (4)	
Needle Cover Separation Force		
Cap Removal Force		

Rationale for the changes:

- *Delivery Time:* (b) (4)
- *Needle cover and cap removal separation force:* (b) (4)

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VI. Outstanding Deficiencies

None

VII. Post-Market Commitments / Post-Market Requirements

None

VIII. Recommendation

Recommendation: Approval

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/s/

JESSICA K LEE
07/12/2017
Signing on behalf of CDRH reviewer

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:	July 7, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761043
Product Name and Strength:	Single ingredient, combination product
Applicant/Sponsor Name:	Benlysta*** (belimumab) injection 200 mg/mL
Submission Date:	June 23, 2017
OSE RCM #:	2016-2224-1
DMEPA Primary Reviewer:	Madhuri R. Patel, PharmD.
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMO

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Benlysta (belimumab) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We note that the proprietary name, Benlysta, is under review for this BLA.

2 CONCLUSION

The revised container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for belimumab injection is acceptable from a medication error perspective. However, we note that the proposed proprietary name, Benlysta, has not been reviewed for this BLA.

[a] Patel M. Label, Labeling, and Human Factors Results Review for Benlysta (b) (4) (BLA 761043). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 31. RCM No.: 2016-2224 and 2016-2225.

***Benlysta is under review for this BLA.

Therefore, we may have additional comments following the review of the proposed proprietary name.

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/s/

MADHURI R PATEL
07/07/2017

SARAH K VEE
07/07/2017

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

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

Memorandum

Date: June 30, 2017

To: Sadaf Nabavian, Pharm.D.
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

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

Subject: BLA 761043
OPDP comments on draft PI, MG, IFU, and carton/container labels for BENLYSTA (b) (4) (belimumab) injection, for subcutaneous use

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Reference is made to DPARP's consult request dated November 4, 2016, requesting review of the proposed Package Insert (PI), Medication Guide (MG), Instructions for Use (IFU), and Carton/Container Labels for BENLYSTA (b) (4) (belimumab) injection, for subcutaneous use.

OPDP has reviewed the proposed draft PI entitled "BLA761043_draft-clean-23JUN2017 (2).doc" that was received via email from Sadaf Nabavian on June 26, 2017. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

OPDP has reviewed the following proposed carton/container labels received via email from Sadaf Nabavian on June 28, 2017:

- draft-200mg-ai-spl-lbl-front-back.pdf
- draft-200mg-ai-trade-lbl-front-back.pdf
- draft-200mg-pfs-spl-lbl-front-back.pdf
- draft-200mg-pfs-trade-lbl-front-back.pdf
- draft-200mg-x-1-ai-rep-ctn.pdf
- draft-200mg-x-1-ai-spl-ctn.pdf
- draft-200mg-x-1-pfs-rep-ctn.pdf
- draft-200mg-x-1-pfs-spl-ctn.pdf

- draft-200mg-x-4-ai-trade-ctn.pdf
- draft-200mg-x-4-pfs-trade-ctn.pdf

The proposed carton labels contain the following dosing information:

> **Dosage:** 200 mg once weekly.
> Refer to Instructions for Use to administer your dose.

The proposed labels omit material information from the DOSAGE AND ADMINISTRATION section of the PI (2.2), including where the dose should be administered. Per 21 CFR 201.55, if it is not possible to present "an informative or useful statement of the recommended or usual dosage in the space available," a more general statement may be used. Therefore, OPDP recommends replacing the proposed presentation with a general statement such as "See Full Prescribing Information for Dosage and Administration."

OPDP also notes that the conditionally approved proprietary name for BLA 761043 is Benlysta (b) (4); however, Benlysta is the name used on the proposed carton/container labels (b) (4). Please ensure that the only the approved proprietary name is used throughout the labeling and labels to avoid any potential discrepancies with promotional materials.

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

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

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

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/s/

KYLE SNYDER
06/30/2017

LABEL, LABELING AND HUMAN FACTORS RESULTS 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:	May 31, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761043
Product Type:	Single ingredient, combination product
Drug Constituent Name and Strength	Benlysta (b) (4) (belimumab) injection 200 mg/mL
Device Constituent:	Autoinjector Pre-filled syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Human Genome Sciences, Inc./GSK
Submission Date:	September 22, 2016
OSE RCM #:	2016-2225
Safety Evaluator:	Madhuri R. Patel, PharmD.
DMEPA Associate Director (Acting):	Mishale Mistry, PharmD., MPH
Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

1 REASON FOR REVIEW

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that DMEPA evaluate the human factors (HF) validation study results, proposed container label, carton labeling, and Prescribing Information (PI) submitted on September 22, 2016, for the proposed Benlysta (b) (4) autoinjector and pre-filled syringe. We previously reviewed the Human Factors protocol and IFU for the autoinjector and prefilled syringe in OSE Review RCM # 2014-768.[a] We note that the name was changed from Benlysta (b) (4) to Benlysta (b) (4) on December 2, 2016 after the label and labeling was submitted and evaluated in OSE Review RCM #2016-10390901[b].

1.1. PRODUCT INFORMATION

Belimumab is currently approved under the proprietary name, Benlysta, is available as 120 mg and 400 mg vials to be used for intravenous infusion. The proposed product, Benlysta (b) (4) (belimumab), is a single-dose autoinjector and pre-filled syringe in 200 mg/mL strength for once weekly subcutaneous administration into the abdomen or thigh. The intended users are healthcare professionals, adult patients for the treatment of adult patients with active, autoantibody positive, systemic lupus erythematosus (SLE) who are receiving standard therapy, and caregivers. See Appendix A for additional details.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] McMillan, T. Human Factors Protocol Memorandum for Benlysta (IND 009970). Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2014 OCT 23. RCM No.: 2014-768.

[b] Patel, M. Proprietary Name Review for Benlysta (b) (4) (BLA 761043). Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2016 DEC 21. RCM No.: 2016-10390901.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

3.1 HUMAN FACTORS VALIDATION STUDY

Human Genome Sciences, Inc. performed a HF validation study to evaluate the safe and effective use of the proposed Benlysta (b) (4) 200 mg/mL autoinjector and prefilled syringe and the associated label, labeling, packaging and Instructions for Use (IFU). DMEPA reviewed the human factors validation study protocols and corresponding Instructions for Use (IFU) for Benlysta (belimumab) autoinjector and prefilled syringe under IND 00997.[c,d]

We note that that the HF validation studies did not include an untrained arm although the intended users are healthcare professionals (HCP), adult patients with SLE who are receiving standard therapy, and caregivers. We also note lay caregivers were not included in the study due to lay caregivers not interacting with the device is significantly different manner than the patient and HCP groups. However, both studies included training decay where the SLE patient user group participants were trained on using the autoinjector or prefilled syringe and then returned the following week to perform an unaided injection. Memory retention is thought to drop to 40% after just 9 hours and further drops to approximately 20% percent around Day 5.[e] Therefore, due to the week-long training decay period for both of these studies, we find the study methodology acceptable without untrained arms and caregiver group.

Autoinjector:

One SLE patient participant committed a use error where they recapped the autoinjector prior to injection. Subjective data from the participant indicated that the user removed the cap, realized she still had preparatory steps to perform (i.e. clean injection site), and placed the cap back on the device until she was ready to inject. According to the study, this did not cause damage to the device or needle, nor did it result in a needle stick injury. This task was categorized as low risk and a precaution about recapping is clearly stated in the IFU. We find that the cautionary statement in the IFU warning against recapping and the needle guard protecting the needle, adequately mitigates the risk of needle stick injury. Recapping is not a new or unique risk seen for such autoinjector products and therefore, we have no additional recommendations to mitigate this risks associated with the recapping error.

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[c] McMillan, T. Human Factors Protocol Review for Benlysta (belimumab)(IND 00997). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 MAY 14. 11 p. OSE RCM No.: 2014-768.

d McMillan, T. Human Factors Protocol Review Memorandum for Benlysta (belimumab)(IND 00997). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 OCT 23. 4 p. OSE RCM No.: 2014-768.

[e] Stahl SM, Davis RL, Kim DH, et al. Play it Again: The Master Psychopharmacology Program as an Example of Interval Learning in Bite-Sized Portions. *CNS Spectrums*. 2010;15(8):491-504.

Prefilled Syringe:

One SLE patient participant did not pinch the injection site prior to needle insertion, which is categorized as an essential task. The study attributed this to the participant having no self-injection experience and being nervous. The participant had remembered to pinch the skin upon completion of the supervised injection. However, for the unaided injection, the participant stated she has no prior self-injection experience and it is not something she is used to doing. When asked to re-read the IFU, she stated she had looked at the step to hold the syringe in one hand and then "blew past" the next (pinch) part. The report states that that after an injection or two this patient would accommodate and not skip this step. If the skin is not pinched prior to injection, the medication would still be delivered, but there is a potential for intradermal or intramuscular delivery. Failure to pinch injection site is not a new or unique risk seen for prefilled syringe injections. We note that the proposed IFU has a clearly marked step and figure depicting pinching of the injection site. Therefore, we do not have any recommendations at this time.

Overall, the human factors validation study results demonstrated that the intended population would be able to use the proposed autoinjector and prefilled syringe safely and effectively.

3.2 LABELS AND LABELING

DMEPA performed a risk assessment of the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. DMEPA finds the prescribing information acceptable from a medication error perspective. However, we note that the labels and labeling can be improved to enhance the readability and prominence of important information (e.g. strength, NDC number) to promote the safe and effective use of the product. We also note that manufacturer information can be added to the syringe labels to allow for correct identification.

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

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the proposed HF validation study report and Prescribing Information acceptable from a medication error perspective. However, our review indicates that from a best practice perspective, the proposed container labels and carton labeling can be improved to increase the readability and prominence of important information. Additionally, we note that the strength can be clarified in the carton labeling, container labels and the IFU. Please see our letter-ready recommendations in Section 4.1 below for the container labels and carton labeling.

4.1 RECOMMENDATIONS FOR HUMAN GENOME SCIENCES, INC.

A. General Comments

FDA issued a final guidance entitled *Nonproprietary Naming of Biological Products* on January 13, 2017 stating the Agency's intention to designate proper names for certain biological products that include distinguishing suffixes. This 351(a) application is within the scope of this guidance. However, the issuing of the guidance occurred at a point in our review of the application that did not allow for sufficient time for FDA to designate a proper name with a suffix, as described in the guidance. Therefore, in order to avoid delaying the approval of the application and in the interest of public health, we will approve the proper name as designated without a suffix, should your BLA be licensed, and intend to work with you post-approval to implement a proper name consistent with the principles outlined in the guidance. We would work with you to minimize the impact this would have to your manufacture and distribution of this product.

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

1. Container label, carton labeling, Instructions for Use (IFU)
    a. Revise the (b) (4) concentration statement to "200 mg/mL" in accordance with the USP General Chapter <1> Injections.
2. Carton Labels
    a. Consider increasing the prominence of the NDC number. Since NDC number is often used as an additional verification prior to drug dispensing in the pharmacy, it is an important safety feature that should be prominently displayed in the top third of principal display panel of the labeling in accordance with 21 CFR 207.35(b)(3)(i).
    b. Consider decreasing the prominence of the statement "Rx Only" to ensure that other important information is not overlooked.
    c. Revise and bold the statement (b) (4) . We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.
    d. As currently presented, there are (b) (4) on the 1-pack and 4-pack autoinjector and prefilled syringe cartons. Since the drug barcode is often used as an additional verification before drug administration in the inpatient setting, the presence (b) (4) is confusing to the healthcare providers. Therefore, we recommend you mov (b) (4) of other required or recommended information on the label per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.

e. Consider moving down the GTIN and S/N numbers away from the Expiration and Lot number to ensure that there are no other numbers located in close proximity to the lot number where it can be mistaken as the lot number.
f. Consider revising the statement under contents on the Principal Display Panel (PDP) for clarity of the net quantity (e.g. (b) (4) Single-Dose 1-mL Autoinjector" instead of (b) (4)). The net quantity should appear on the PDP per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
g. For the autoinjector, add a statement "Single-dose autoinjector" to clarify how the medication should be safely handled per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
h. For the prefilled syringe, while the container is too small or otherwise unable to accommodate all information, the name of the manufacturer, packer, or distributor of the drug is still required in accordance with 21 CFR 201.10(i).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Benlysta [(b) (4)] that Human Genome Sciences, Inc. submitted on September 22, 2016.

Table 2 presents relevant product information for Benlysta [(b) (4)] that Human Genome Sciences, Inc. submitted on September 22, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Benlysta [(b) (4)] (belimumab) and the Listed Drug		
Product Name	**Benlysta [(b) (4)]**	**Benlysta**
Initial Approval Date	N/A	March 9, 2011
Active Ingredient	belimumab	belimumab
Indication	Treatment of systemic lupus erythematous (SLE)	Treatment of systemic lupus erythematous (SLE)
Route of Administration	Subcutaneous	Intravenous
Dosage Form	Injection	Injection
Strength	200 mg	120 mg, 400 mg
Dose and Frequency	200 mg administered subcutaneously once weekly	10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter
How Supplied	[(b) (4)] single-dose autoinjector with 27-gauge, half-inch needle attached [(b) (4)] single-dose prefilled glass syringe with 27-gauge, half-inch needle attached	Sterile, preservative-free, lyophilized powder for reconstitution, dilution, and intravenous infusion provided in single [(b) (4)] glass vials with a rubber stopper (not made with natural rubber latex) and a flip-off seal. Each 5-mL vial contains 120 mg of belimumab. Each 20-mL vial contains 400 mg of belimumab. 5 mL and 20 ML
Storage	Refrigerated [(b) (4)] 2°C to 8°C (36°F to 46°F) and protected from light. Keep the product in the original carton to protect from light until the	Refrigerated at 2˚C to 8˚ C (36˚ to 46˚ F) [(b) (4)] protected from light and stored in the original carton until use. Do not

	time of use. Do not freeze. Do not shake. Avoid exposure to heat. Do not use if left out (b) (4) for more than 12 hours.	freeze. Avoid exposure to heat. (b) (4)
Container Closure	n/a	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On January 11, 2017, we searched the L:drive and AIMS using the terms, Benlysta and Belimumab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 10 previous reviews. We identified 4 previous proprietary name reviews and 4 previous label and labeling reviews not relevant to this review. We also identified 2 previous human factors protocol reviews and we confirmed that our previous recommendations were implemented[f,g].

[f] McMillan, Teresa. Human Factors Protocol Review for Benlysta (belimumab)(IND 00997). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 May 14. 11 p. OSE RCM No.: 2014-768.

[g] McMillan, Teresa. Human Factors Protocol Memorandum for Benlysta (belimumab)(IND 00997). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2014 Oct 23. 4 p. OSE RCM No.: 2014-768.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design

Autoinjector

Summary of preliminary analyses and evaluations, including formative studies

- **Formative Study 1:** Evaluation of Autoinjector Platforms and Features
  - Key User Requirements Found:
    - Appropriate size to provide acceptable grip but not too large such that the device is visually unappealing or intimidating to use
    - Larger features/grips to assist in cap removal
    - Intentional activation that is simple and easy to use. A button can provide the needed activation intention and control over injection but presented ergonomic challenges for some users.
    - Simple operation with the fewest number of steps (two operational steps preferred).
    - Intuitive device orientation to prevent confusion regarding which end possesses the needle and whether or not there is a button to press.
    - Device should provide various types of feedback to provide assurance of correct use. Audible indicators signifying start and end of injection are preferred but must be loud enough to hear while not too loud so as to startle the user.
    - Larger inspection windows are preferred to enable visibility of drug solution and monitoring of dosing.
- **Formative Study 2:** Final Selection of Autoinjector Platform and Identification of User Requirements and Industrial Design
  - Possessed Optimal Features in the following:
    - Simple two-step operation
    - Press-on activation (no-button)
    - Manual needle insertion
    - Start and end-of-dose clicks (at appropriate sound level)
    - Large inspection window
    - Easy cap removal
    - Small size which permits modification of the form to the optimal ergonomic shape
  - Form of the Autoinjector was customized to a “pillow” shape (i.e. a pinched-oval cross section) with a ring-shaped cap
    - Aesthetically pleasing and ergonomically preferred
    - Clean and simple design increased the intuitiveness of use, particularly with respect to orientation of the device (i.e. identification of the needle end) and the clarity that there is no activation button.
    - Ring- shaped cap provided an improved grip and met the ergonomic needs of the patients during cap removal
- **Formative HF Study 3:** Confirmation of Autoinjector Design and Optimization of IFU
    - Several potential optimizations to the IFU were identified including the instructions defining the end of dose.

- With regard to packaging, top-opening cartons were preferred over side-opening cartons so that the contents can be accessed easily.
- Smaller packaging was also preferred considering patient storage of devices in a home refrigerator.

Pre-filled Syringe

Summary of preliminary analyses and evaluations, including formative studies

- **Formative Study 1 and 2:** Evaluation of Safety Syringe Platforms and Features
  - (b) (4) Safety syringe
    - Easiest to inject in terms of the perceived required force, an important attribute for a viscous drug and for SLE patients with potential dexterity issues.
    - The safety mechanism deploys automatically (passively) at the end of the injection and requires little thought or additional action from the user.
  - (b) (4)
    - Add-on finger flange enhanced the experience and provided a more confident handling of the syringe and a more comfortable injection
      - Provided counter-leverage that reduced the amount of strength required to push down the plunger
      - Also influenced some to change from an index finger to a thumb injection posture.
- **Formative HF Study 3:** Confirmation of Safety Syringe Design and Optimization of IFU
  - All participants were able to successfully inject and activate the safety mechanism.
  - Participants did not have any difficulty understanding the IFU
  - Several minor optimizations were identified.

Risk Analysis

Risk Severity	Use Error and Potential Clinical Impact
High	May result in death, life threatening injury, permanent impairment or unknown severe effect. May have significant impact on therapeutic effect (*e.g.* repeated missed dose or repeated under dose). May affect biologic product quality with unknown clinical impact.
Med	May result in injury or impairment requiring professional medical intervention. May have minimal impact on therapeutic effect (*e.g.* correctable missed dose or under dose).
Low	May result in temporary injury or impairment not requiring professional medical intervention, inconvenience, temporary discomfort or patient complaint.

"Level of current risk severity "High" (or critical), "Medium" (essential, but not immediate to user), and "Low" risk. "

Autoinjector

Task	Risk Severity	Clinical Impact	Implemented Risk Mitigation
Autoinjector storage	High	Prolonged exposure to temperatures outside 2-8°C may affect biologic product quality with unknown clinical impact. Freezing may impact container closure integrity.	Dedicated section in IFU with bold text for section entitled "Important Storage Information". Instructions on outer packaging. Training
Gather supplies other than autoinjector	Low	No immediate clinical impact. Clinical impact of not using supplies is captured in the relevant tasks below (*i.e.* not using alcohol swab or sharps disposal container).	Dedicated section in IFU with text and illustrations of required supplies.
Identification of expiration date	High	Expired product may contain degradants and may affect biologic product quality with impact not fully evaluated in clinical trials.	Dedicated section in IFU with text and illustrations showing where the expiration date is located on the device. Training
Allow autoinjector to warm up before use	Low	Improper warm up may lead to longer injection time or uncomfortable injection.	Dedicated section in IFU with text and illustrations indicating the need to allow the device to warm up (illustration of clock). Warm-up and stability studies to understand limits of warm up period.
Open blister pack[1]	Low	Failure to open blister may result in patient complaint	Dedicated statement in IFU with text.
Remove device from blister pack[1]	Low	Failure to open blister may result in patient complaint	Dedicated statement in IFU with text.
Drug product inspection	High	Atypical product appearance suggests degradants which may impact biologic product quality with impact not fully evaluated in clinical trials.	Dedicated section in IFU with text, symbols and illustrations showing where drug product is visible for inspection. Training
Identification of injection site	High	Potential to impact drug absorption and pharmacokinetics with impact not fully evaluated in clinical trials.	Dedicated section in IFU with text, symbols and illustrations of acceptable injection sites. Training
Cleaning of injection site	Low	Improper or omission of cleaning may lead to local infection at injection site.	Dedicated section in IFU with text, symbols and illustrations showing cleaning of injection site.

Task	Risk Severity	Clinical Impact	Implemented Risk Mitigation
Removal of Ring Cap	Medium	Failure to remove the Ring Cap may result in missed dose but is detectable and therefore correctable. Potential for needle stick injury.	Ring Cap designed for ease of removal. Dedicated section in IFU with text, symbols, and illustrations showing how to remove cap with emphasis on not removing until ready to inject. Needle drying study to set appropriate time limit for Ring Cap removal Training
Start of injection	High	Missed or under dose may occur if patient fails to start the injection properly. If repeated, there is the potential for reduced therapeutic effect. Potential for needle stick injury.	Activation spring selected with appropriate force required to start injection. First click at start of injection. Dedicated section in IFU with text, symbols and illustrations showing how to position device and how to initiate activation on injection site. Training
Completion of injection	High	Under dose may occur if patient fails to complete the injection properly. If repeated, there is the potential for reduced therapeutic effect.	*Based on empirical testing, the delivered dose after the 2nd click meets the release specification for deliverable volume ((b) (4) (b) (4)mL) and is approximatelv (b) (4)mL ((b) (4)% of the deliverable volume) (b) (4) than when the purple indicator has stopped moving. This difference is clinically negligible considering exposure variability from body size and other unique patient characteristics (e.g. injection site anatomy, clearance rates, etc.).*Dedicated section in IFU with text and illustrations showing the relationship of clicks and purple indicator movement when confirming end of injection. Training
Autoinjector disposal	Medium	Accidental needle stick to patient or other person in household or waste stream, cross-contamination or infection. The Needle Guard feature of the device mitigates this risk.	Needle Guard designed to prevent needle access. Dedicated section in IFU with text, symbols and illustrations showing proper disposal. Training

[1]Task was not included in the original protocol

Pre-filled Syringe

IFU Step	Risk Severity	Clinical Impact	Implemented Risk Mitigation
Safety syringe storage	High	Prolonged exposure to temperatures outside 2-8ºC may affect biologic product quality with unknown clinical impact. Freezing may impact container closure integrity.	Dedicated section in IFU with bold text for section entitled "Important Storage Information". Instructions on outer packaging. Training
Gather supplies other than safety syringe	Low	No immediate clinical impact. Clinical impact of not using supplies is captured in the relevant tasks below (*i.e.* not using alcohol swab or sharps disposal container).	Dedicated section in IFU with text and illustrations of required supplies.
Identification of expiration date	High	Expired product may contain degradants and may affect biologic product quality with impact not fully evaluated in clinical trials.	Dedicated section in IFU with text and illustrations showing where the expiration date is located on the device. Training
Allow safety syringe to warm up before use	Low	Improper warm up may lead to longer injection time, higher injection forces and/or uncomfortable injection.	Dedicated section in IFU with text and illustrations indicating the need to allow the device to warm up (illustration of clock). Warm-up and stability studies to understand limits of warm up period.
Open blister pack[1]	Low	Failure to open blister may result in patient complaint	Dedicated statement in IFU with text.
Remove device from blister pack[1]	Low	Failure to open blister may result in patient complaint	Dedicated statement in IFU with text.
Drug product inspection	High	Atypical product appearance suggests degradants which may impact biologic product quality with impact not fully evaluated in clinical trials.	Dedicated section in IFU with text, symbols and illustrations showing where drug product is visible for inspection. Training
Identification of injection site	High	Potential to impact drug absorption and pharmacokinetics with impact not fully evaluated in clinical trials.	Dedicated section in IFU with text, symbols and illustrations of acceptable injection sites. Training

IFU Step	Risk Severity	Clinical Impact	Implemented Risk Mitigation
Cleaning of injection site	Low	Improper or omission of cleaning may lead to local infection at injection site.	Dedicated section in IFU with text, symbols and illustrations showing cleaning of injection site.
Removal of Needle Cap	Medium	Failure to remove the Needle Cap may result in missed dose but is detectable and therefore correctable. Potential for needle stick injury.	Dedicated section in IFU with text, symbols and illustrations showing how to remove cap with emphasis on not removing until ready to inject. Needle drying study to set appropriate time limit for Needle Cap removal Training
Pinch around injection site[2]	Medium	Potential intradermal or intramuscular delivery.	Dedicated section in IFU with text, symbols and illustrations showing how to insert the needle. Training
Insertion of needle[2]	High	Missed or under dose may occur if patient fails to insert the needle properly. If repeated, there is the potential for reduced therapeutic effect. Potential for needle stick injury.	Dedicated section in IFU with text, symbols and illustrations showing how to insert the needle. Training
Completion of injection[3]	High	Under dose may occur if patient fails to complete the injection properly. If repeated, there is the potential for reduced therapeutic effect.	Dedicated section in IFU with text and illustrations showing the how to complete the injection and activation of needle safety mechanism. Training
Syringe safety activation[3]	Low	Potential for needle stick injury.	Dedicated section in IFU with text and illustrations showing the how to complete the injection and activation of needle safety mechanism. Training
Safety syringe disposal	Medium	Accidental needle stick to patient or other person in household or waste stream, cross-contamination or infection. The needle safety mechanism of the device mitigates this risk.	Needle Guard designed to prevent needle access. Dedicated section in IFU with text, symbols and illustrations showing proper disposal. Training

[1]Task was not included in the original protocol

[2]Original protocol grouped these tasks under "Start of Injection" step with combined high risk severity. Prior to study execution, these tasks were separated and assigned medium and high risk severity respectively.

[3]Original protocol grouped these tasks under "Completion of Injection" step with combined high risk severity. Prior to study execution, these tasks were separated and assigned high and low risk severity respectively.

Autoinjector and Prefilled Syringe

Intended Product Users

- SLE patients who would use the device for weekly self-administration of BENLYSTA® (belimumab)
- HCPs who would train patients on how to use the device or administer the injection in the treatment of adult patients with active autoantibody-positive SLE

Uses

- Treatment of adult patients with active autoantibody-positive SLE
- Subcutaneous injection into thigh or abdomen

Use Environments

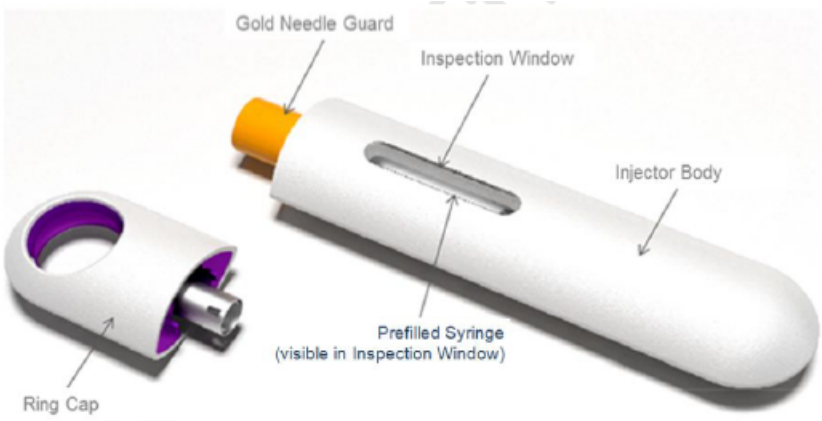
- Intended for weekly at-home self-administration
- Healthcare setting (for HCP)

Training

Expected that a patient will be provided training by their HCP upon initiation of their medication and prior to first self-injection

Product User Interface

- Autoinjector

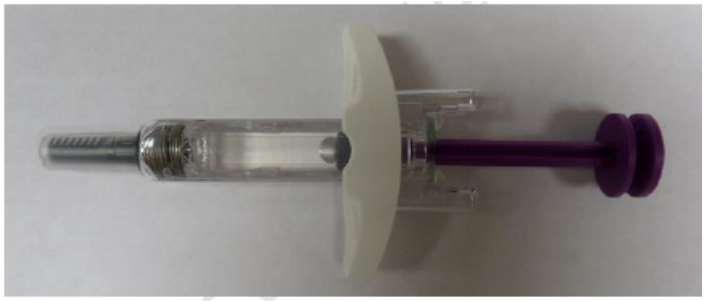


BENLYSTA® (belimumab) Autoinjector

  - Fully mechanical, hand-held, single-dose, prefilled, disposable device
  - Designed for manual needle insertion, automatic delivery of the drug product, manual needle withdrawal and automatic needle guarding
  - Utilizes one mL long glass prefilled syringe containing the liquid drug product with a 27G x ½" (b) (4) staked needle
  - Prior to use of the autoinjector, the syringe needle is shielded from the user by a Gold Needle Guard to hide the needle and prevent accidental contact with the

needle. Once the user removes the Ring Cap and presses the autoinjector on the intended injection site (thus depressing the Gold Needle Guard and manually inserting the needle to the controlled insertion depth), the autoinjector automatically delivers the entire contents of the prefilled syringe (b) (4) Visual indicators viewable in the Inspection Window (Purple Indicator/plunger rod movement) and audible/tactile indicators (clicks) inform the user of proper use of the autoinjector including the start and end of injection.

- Following injection, as the user manually removes the needle from the injection site, the Gold Needle Guard automatically shields the syringe needle and locks it in place to prevent accidental needle sticks. The user is instructed to dispose of the used autoinjector in an appropriate sharps disposal container and treat the injection site as needed.

- Pre-filled Syringe
  - 
    BENLYSTA® (belimumab) safety syringe with safety and finger flange
  - 
    UltraSafe Plus Syringe Body
    
    Large and Concaved Thumb Pad
    
    Finger Flange
  - 1 mL long glass BENLYSTA® safety syringe (containing liquid drug product with a 27G x ½" (b) (4) staked needle) which is assembled into the (b) (4) Needle Guard
  - (b) (4) device with add-on finger flange
  - Once user removes needle cap and inserts the needle into the intended injection site, the user delivers the full dose of the drug by leveraging the extended finger flange and pressing the plunger rod all the way down.
  - Following injection, as the user manually removes the needle from the injection site and removes their thumb/finger from the plunger rod, the needle safety guard is activated and automatically retracts the needle into the syringe housing. The needle locks in place to prevent accidental needle sticks. The user is instructed to dispose of the used BENLYSTA® safety syringe in an appropriate sharps disposal container and treat the injection site as needed.

Summary of known use problems with previous models or similar products

Autoinjector

- **Automated Features:**
  - Automated dispensing of the drug product after manual insertion of the needle. Manual needle insertion addresses known use issues associated with existing auto-needle insertion devices (b) (4)
  - Device has automated shielding of the needle immediately following manual removal of the needle from the injection site. Existing devices with manually activated shielding may not be shielded by users as this can be viewed as an extra and unnecessary step.
- **Cap Removal:** One challenging manipulation of an autoinjector is removal of the needle cap which can require a difficult pinching motion with the fingers to grip the cap and a high pull-off force inherent in the prefilled syringe needle shield which maintains container closure of the primary drug container. To address this, the autoinjector was designed with a large Ring Cap enabling the user to employ an index finger or thumb to remove the cap instead of a challenging pinching technique. In addition to the large ring, a capping feature was included on the cap/body interface that gives the user the option of removing the Ring Cap by rotating it (instead of pulling) which requires less strength on the part of the user.
- **Device Activation:** The autoinjector was designed so that an explicit action is required to activate the injection thus mitigating the risk of unintentional activation. Activation is initiated without requiring a button. Button activation is a common autoinjector feature but has been shown to be challenging for users with hand dexterity and strength issues.
- **Injection Status Feedback:** The design of the autoinjector provides the user with both visual and audible/tactile feedback to indicate initiation and completion of the injection. The Inspection Window was designed to be as large as possible to allow for good visibility.
- **Needle Safety:** After injection, when the needle is removed from the skin, the Gold Needle Guard automatically extends back over the needle and locks to protect the user and anyone in the waste stream from needle stick injury.
- **Intuitive Orientation:** The simple and clean design of the autoinjector enables intuitive use in terms of orientation and mitigation of confusion regarding which end contains the needle. The nonneedle end of the autoinjector is designed with a shape and cleanliness (i.e. no markings) that clearly indicates that there is no function. In addition, a simple color scheme is employed to further enable intuitiveness as the Needle Guard is the only part of the autoinjector with color relative to the all-white body.
- **Hand-Held Comfort and Grip**: Establish a body form that addresses known issues for devices employing small diameters in disease indications where dexterity and hand strength are compromised. The results of the formative studies yielded a novel “pillow”

shape cross-section which provides increased gripping area (longer width of the body cross-section) while not making the device too large overall (inclusion of shorter width of the body cross-section). In addition to providing sufficient area for grip, this body form closely fits the contour of a closed fist and is natural to hold in a closed fist grip. While a closed fist grip is the suggested holding technique, it was observed in the formative studies that the autoinjector form supports a wide variety of gripping techniques.

Pre-filled Syringe

- (b) (4) **Syringe with Needle Safety Guard:** A standard pre-filled syringe poses a risk of needle prick post-injection due to exposure after removing from the body up to insertion into sharps container. As part of the formative studies conducted with this syringe, different syringe bodies were compared. It was determined that the (b) (4) safety syringe was the most comfortable and easiest to use for SLE patients, without adding unnecessary steps to the procedure. This syringe body provides the ability for the user to deliver the full dose of the drug, passively activate the syringe safety at the bottom of the throw, and retract the needle into the syringe housing while still on site.
- **Plunger Thumb Pad Shape and Size:** A standard pre-filled syringe plunger thumb pad can be difficult for some users to manipulate, especially those with conditions which entail strength and dexterity issues. It was determined that a larger and concaved thumb pad gave participants the greatest amount of control and comfort while performing the injection.
- **Finger Flange:** A standard prefilled syringe does not provide enough finger stability for a user population that has strength and dexterity issues. Added finger flange improves stability and handling, added leverage that is vital when injecting a viscous medication, instills confidence in the user, as it is a more manageable product with more surface area to hold onto.

Objective:

1. Demonstrate that the autoinjector/safety syringe, associated IFU, packaging and labeling 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.
2. Identify any aspects of the autoinjector/safety syringe design, injection procedure or IFU which may lead to confusion, failures, high-risk errors or patient safety risks.
3. Validate the autoinjector/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.

Methods:

Autoinjector

Simulated use human factors validation study involving a total of 30 participants divided into two user groups

User Groups

A total of 30 participants were included in the study from the two user groups identified.

- **User Group 1 (SLE Patient):** Fifteen patients who have been diagnosed with SLE and represent the high-risk user population.
- **User Group 2 (HCPs):** Fifteen HCPs who treat SLE patients and would train patients on use of the autoinjector were included in the study.

User Groups	Number of Participants
SLE patients (trained)	N = 15 (50%)
HCPs (self-trained)	N = 15 (50%)
Total	**N = 30 (100%)**

Participant Training

There were two training groups in the study. Half of the participants (15/30, 50%) were trained SLE patients while the other half (15/30, 50%) did not receive training (Untrained HCPs).

- **Trained:** All SLE participants (N=15) were trained during their first session, which is consistent with the procedure that would occur if a patient were actually prescribed to take BENLYSTA® (belimumab) with an autoinjector for the first time. All trained participants also performed a single supervised injection as part of training.
  - **Enrollment Eligibility:** At the conclusion of training, the trainer completed an enrollment form (see Appendix I). Participants were deemed not eligible for the remainder of the study if they demonstrated one or more of the following extreme (outlier) training outcomes: extremely low acuity/cognitive ability suggestive of a person who would not, or should not, be prescribed

self-injection, extreme levels of fear, anxiety, frustration or workload that would likely prevent the patient from using the autoinjector correctly, or if the participant was not willing to use the device in a safe manner (non-compliance). All patient participants in this study were deemed eligible and passed training (see Appendix J for Enrollment Form Summary).

- **Untrained:** All HCP participants (N=15) did not receive any form of training during the study. Instead all HCP participants were given time to familiarize themselves with the device prior to performing their unaided injections.

Number of Study Sessions

All SLE patient participants participated in two study sessions.

- **Session 1:** During their first session all SLE patient participants received training and performed their supervised injection. All SLE patient participants also placed a device in the refrigerator to support the context of the second session.
- ***Session 2:*** All SLE patients came back for a second session the following week, from 4-7 days after their training session. On average the decay time between training and unaided use was 5.5 days. The second session comprised of participants answering a series of knowledge probe questions, performing an inspection task, followed by an unaided injection trial. Participants were also asked to provide feedback on the IFU at the end of the session.

SLE Participant Session Overview				
Session 1 (Training)		**Session 2 (The following week)**		
Training	Supervised injection followed by placement of device in refrigerator	Knowledge Probes and Inspection Tasks	Unaided Injection followed by post-interaction questions	IFU Feedback
Context: Doctor's office		**Context:** Home with ambient noise (*e.g.* Radio)		

All HCP participants participated in a single study session.

- **Single Session:** During their single session all HCP participants first self-trained or familiarized themselves with the device and IFU. HCPs then were asked a series of knowledge probe questions and asked to perform several inspection tasks. Participants then performed two unaided injection trials and provided feedback on the IFU.

HCP Participant Session Overview				
Single Session				
Self-Training/ Familiarization	Knowledge Probes and Inspection Tasks	Unaided Injection 1 followed by post-interaction questions	Unaided Injection 2 followed by post-interaction questions	IFU Feedback
Context: Hospital or doctor's office setting with ambient noise (*e.g.* Hospital)				

Supervised and Unaided Injections

A total of fifteen (15) supervised and forty-five (45) unaided injections were performed by participants during the study.

- All SLE participants performed a single supervised injection during training and a single unaided injection during their second study session for a total of fifteen (15) supervised injections and fifteen (15) unaided injections completed by SLE patient participants.
- All HCP participants performed two unaided injections during their single study session for a total of thirty (30) unaided injection performed by HCPs.

User Groups	Injections
SLE patients (trained)	15 Supervised 15 Unaided
HCPs (self-trained)	30 Unaided
Total	**60 total injections**

Summary:

	User Group 1		User Group 2	
N	N=15		N=15	
User Type	SLE Patients		HCPs	
Training Group	Trained		Untrained	
Study Sessions	2 Sessions		1 Session	
Injections	1 Supervised and 1 Unaided		2 Unaided	
Injection Sites	Abdomen (N=8)	Thigh (N=7)	Abdomen (N=7)	Thigh (N=8)

Pre-filled Syringe

Simulated use human factors validation study involving a total of 30 participants divided into two user groups

User Groups

A total of 30 participants were included in the study from the two user groups identified.

- **User Group 1 (SLE Patients):** Fifteen patients who have been diagnosed with SLE and represent the high-risk user population.
- **User Group 2 (HCPs):** Fifteen HCPs who would treat SLE patients and would train patients on use of the BENLYSTA® safety syringe were included in the study.

User Groups	Number of Participants
SLE patients (trained)	N = 15 (50%)
HCPs (self-trained)	N = 15 (50%)
Total	**N = 30 (100%)**

Participant Training

There were two training groups in the study. Half of the participants (15/30, 50%) were trained SLE patients while the other half (15/30, 50%) did not receive training (Untrained HCPs).

- **Trained:** All SLE Patient Participants (N=15) were trained during their first session, which is consistent with the procedure that would occur if a patient were actually prescribed to take BENLYSTA® (belimumab) with a safety syringe for the first time. All trained participants also performed a single supervised injection at the conclusion of the training session in order to demonstrate safety and competency.
  - **Enrollment Eligibility:** At the conclusion of training, the trainer completed an enrollment form (see Appendix I). Participants were deemed not eligible for the remainder of the study if they demonstrated one or more of the following extreme (outlier) training outcomes: extremely low acuity/cognitive ability suggestive of a person who would not, or should not, be prescribed self-injection, extreme levels of fear, anxiety, frustration or workload that would likely prevent the patient from using the BENLYSTA® safety syringe correctly, or if the participant was not willing to use the device in a safe manner (non-compliance).
  - All patient participants in this study were deemed eligible and passed training (see Appendix J for Enrollment Form Summary).

*Note that one patient (b) (6) dropped out after training due to a severe Lupus flair-up. This participant was replaced (b) (6) by a patient who was trained and then returned 24 hours (1 day) later.

- **Untrained:** All HCP participants (N=15) did not receive any form of training during the study. Instead all HCP participants were given time to familiarize themselves with the syringe and procedure, as they saw fit, prior to performing their unaided injections.

Number of Study Sessions

All SLE patient participants participated in two study sessions.

- **Session 1:** During their first session all SLE patient participants received training and performed their supervised injection. All SLE patient participants also placed a carton in the refrigerator to support the context of the second session.
- ***Session 2:*** All participants came back for a second session the following week, from 3-7 days after their training session. On average the decay time between training and unaided use was 5.5 days. . The second session consisted of participants answering a series of knowledge probe questions, performing a drug and expiration date inspection task, performing an unaided injection trial, and providing feedback on the syringe, procedure and IFU.

SLE Patient Participant Session Overview				
Session 1 (Training)		Session 2 (The following week)		
Training	Supervised Injection followed by placement of device in refrigerator	Knowledge Probes and Inspection Tasks	Unaided Injection followed by post-interaction questions	IFU Feedback
Context: Doctor's office		**Context:** Home with ambient noise (*e.g.* TV)		

All HCP participants participated in a single study session.

- **Single Session:** During their single session all HCP participants first familiarized themselves with the syringe and IFU. They then answered a series of knowledge probe questions, performed a drug and expiration inspection task, performed two unaided injection trials (separated by a break), and provided feedback on the syringe, procedure and IFU.

HCP Participant Session Overview				
Single Session				
Self-Training/ Familiarization	Knowledge Probes and Inspection Tasks	Unaided Injection 1 followed by post-interaction questions	Unaided Injection 2 followed by post-interaction questions	IFU Feedback
Context: Hospital or doctor's office setting with ambient noise (*e.g.* Hospital)				

Supervised and Unaided Injections

A total of fifteen (15) supervised and forty-five (45) unaided injections were performed by participants during the study.

User Groups	Injections
15 SLE Patients (trained)	15 Supervised 15 Unaided
15 HCPs (self-trained)	30 Unaided
Total	60 total injections

Summary:

	User Group 1		User Group 2	
N	N=15		N=15	
User Type	SLE Patients		HCPs	
Training Group	Trained		Untrained	
Study Sessions	2 Sessions		1 Session	
Injections	1 Supervised and 1 Unaided		2 Unaided	
Injection Sites	Abdomen (N=8)	Thigh (N=7)	Abdomen (N=7)	Thigh (N=8)

Data collection:

The measurement plan included the Human Factors triad of measurements - performance, behavior and subjective experience.

During each session, IAA personnel observe the behaviors on each of the multiple steps, and recorded successes and failures, errors, confusions, and other indices of mal-interaction that could result in incorrect use of the device. After each task or knowledge probe, participants were actively probed to provide a subjective narrative on ease of use and any difficulties or concerns in using the device.

Performance Measures

IAA test personnel observed participants during each dosing trial and recorded their performance along a number of measures, as well as any unanticipated errors or events. Refer to the test protocol in Appendix F for all performance measures collected.

Behavioral Measures

Behavioral measures included verbal comments made by the participant during the study (when applicable) and their reactions to the device. Behavioral measures also included reference materials used by the participant during each dosing trial. Refer to the test protocol in Appendix F for all behavioral measures collected.

Subjective Measures

After performing each unaided trial, participants provided subjective feedback related to their interaction with the product and IFU. Refer to the test protocol in Appendix F for all subjective measures collected.

Autoinjector

Overall performance success is achieved when the user fully prepares and administers their dose without making any preventable use errors that could result in serious injury to the patient. Further, success is defined at the more micro task level in Table 6.2c below. Our measurement plan included observing pass/fail criteria for all sub-tasks, as well as observing behavior (errors, close calls, difficulties) and subjective narrative responses relevant to critical steps. Any errors or failures were followed up with a subjective debrief with the participant.

6.2c Tasks with Study Technique, Range of Acceptable Performance/Response

Task	Risk Severity	Study Technique	Range of Acceptable Performance or Response
Autoinjector storage	High	**Subjective response data:** Knowledge probes Participant was asked to state how the product should be stored. Participant was asked if they can freeze the product.	Must answer to store refrigerated. Must answer "No".
Gather supplies other than autoinjector	Low	**Subjective response data:** Knowledge probe Participant was asked what supplies are needed for injection.	Must respond alcohol swab and sharps container (gauze pad or cotton ball optional).
Identification of expiration date	High	**Objective performance data:** Task Participant was asked to identify expiration date.	Must identify expiration date on autoinjector label.
Allow autoinjector to warm up before use	Low	**Subjective response data:** Knowledge probe Participant obtained a device from the refrigerator for their unaided trial and was asked what should be done with the device before the injection.	Must state that they would let the device warm to room temperature for at least 30 minutes.
Open blister pack[1]	Low	**Objective performance data:** Task Participant was observed regarding opening the blister pack.	Must open blister pack.
Remove autoinjector from blister pack[1]	Low	**Objective performance data:** Task Participant was observed regarding removing the device from blister pack.	Must remove autoinjector from blister pack.
Drug product inspection	High	**Objective performance data:** Task Participant was asked to inspect the drug	Participant inspects drug through Inspection Window.
		Subjective response data: Knowledge probe Participant was asked to identify if drug is good or degraded and state why. Feedback Participant commented on any difficulty inspecting drug through the window.	Must know what good drug looks like (clear and colorless with no particles). N/A

Task	Risk Severity	Study Technique	Range of Acceptable Performance or Response
Identification of injection site	High	**Subjective response data:** Knowledge probe Participant was asked to state the allowable injection sites before any pad is applied to their body.	Must respond abdomen and/or thigh
Cleaning of injection site	Low	**Objective performance data:** Task Participant was observed regarding cleaning of the injection site.	Must clean injection site with alcohol swab
Removal of Ring Cap	Medium	**Objective performance data:** Task Participant was observed regarding their ability to remove the Ring Cap.	Must remove Ring Cap without injury and < 15[1] minutes before injection
		Subjective response data: Feedback Participant commented on any difficulty removing Ring Cap.	N/A
Activation of injection	High	**Objective performance data:** Task Participant was observed regarding their ability to start the injection	Must activate autoinjector by pressing down Gold Needle Guard on injection site. Injection angle must be approximately perpendicular to injection surface.
		Subjective response data: Knowledge probe Participant was asked to state how he/she knew the injection had started Feedback Participant commented on any difficulty starting the injection	Must identify one of the following initiation feedbacks: First click (audible or tactile) or Purple Indicator movement (visual) N/A
Completion of injection	High	**Objective performance data:** Task Participant was observed regarding delivery of the full dose	Must not remove device from injection site until injection is complete (after second click or after Purple Indicator stopped moving).
		Subjective response data: Knowledge probe Participant was asked to state how he/she knew the injection was complete.	Must state heard/felt second click or waited until Purple Indicator stopped moving.
Autoinjector disposal	Medium	**Objective performance data:** Task Participant was observed regarding autoinjector disposal.	Must place used autoinjector into Sharps Container.

[1]Revised from submitted protocol based on needle tip drying technical study completed after submission

6.3 Technique for Capturing Unanticipated Use Errors

All use errors observed which were not included in the risk analysis were documented. Testing staff was in close observation of the participant during the entire training and injection procedures in order to capture any unanticipated mal behaviors. In addition, recording equipment was utilized to capture any questionable behaviors and enable post-study video analysis. Participants were debriefed on any of these unanticipated use errors.

The following are potential user actions that are not part of normal use of the product and are not expected but may occur as anticipated via the risk assessment and human factors expert review. These are listed in the table below and were observed for occurrence during the study.

Unexpected Actions	Risk Severity	Clinical impact	Study Technique (Objective Performance Data)	Implemented Risk Mitigation
Pre-injection tampering	High	May result in needle stick to patient or other person in household, potential loss of dose, injection site infection or cross contamination.	Participants were observed regarding tampering or interaction with the device.	Packaging included tamper evident features.
Drops autoinjector	Low	May result in extended delivery time.	Participants were observed regarding instances of dropping the device before administering the injection. If the subject drops it, they were observed regarding whether or not they continue to use that device.	Dedicated section in IFU with bold text and symbols stating the device should not be used if dropped. Drop testing conducted in accordance with ISO11608-1 demonstrating minimal impact on device performance and no impact on product quality.
Shakes autoinjector	Medium	Shaking may impact biologic product quality with unknown therapeutic consequences.	Participants were observed regarding instances of shaking the device before administering the injection.	Dedicated section in IFU with bold text and symbols stating not to shake product. Shaking studies performed to demonstrate product is not sensitive to shaking.
Recaps autoinjector before injection	Low	May result in needle stick or damaged needle and painful injection.	Participants were observed regarding instances of recapping the needle with the Ring Cap before administering the injection.	Dedicated section in IFU with bold text and symbols clearly stating for participant not to recap the device before injection.
Inverts autoinjector to administer injection	Medium	Missed dose. User should be aware of failure and it is therefore correctable.	Participants were observed regarding any instances of removing the cap and inverting the device to administer the injection.	Design of device intended to be clear which end contains the needle including distinct yellow color against all white body. Device end without needle designed to be very clean with minimal markings. Dedicated sections in IFU with bold text, symbols and illustrations showing proper orientation of device during use.
Unintentional activation during handling	Medium	Missed or under dose. User should be aware of failure and it is therefore correctable.	Participants were observed for unintentional activation of device.	(b) (4) (b) (4) Dedicated sections in IFU with bold text, symbols and illustrations.
Needle stick injury	Low	Needle stick injury with temporary patient discomfort or complaint.	Participants were observed for any needle stick injuries or close calls during the entire session.	Needle Guard is designed to protect against unintentional needle access after use
Post injection tampering	Low	May result in needle stick injury with temporary patient discomfort or complaint.	Participants were observed for any tampering or interaction with the device.	Needle Guard is designed to lock and protect against unintentional needle access after use.

Prefilled Syringe

Overall performance success is achieved when the user fully prepares and administers their dose without making any use errors that could result in serious injury to the patient. Further, success is defined at the more micro task level in the Table 6.2c below. Our measurement plan included observing pass/fail criteria for all sub-tasks, as well as observing behaviors (errors, close calls, difficulties) and subjective narrative responses relevant to critical steps. Any errors or failures were followed up with a subjective debrief with the participant.

6.2c Tasks with Study Technique, Range of Acceptable Performance/Response

IFU Step	Risk Severity	Study Technique	Range of Acceptable Performance or Response
Safety syringe storage	High	**Subjective response data:** Knowledge probes Participants were asked to state how the product should be stored. Participants were asked if they can freeze the product.	Must answer to store refrigerated. Must answer "No".
Gather supplies other than safety syringe	Low	**Subjective response data:** Knowledge probe Participants were asked what supplies are needed for injection.	Must respond alcohol swab and sharps container (gauze pad or cotton ball optional).
Open syringe blister pack	Low	**Objective performance data:** Task Participants were asked to identify expiration date.	Must open syringe blister pack.
Remove syringe from blister pack	Low	**Objective performance data:** Task Participants were asked to identify expiration date.	Must remove syringe from blister pack.
Identification of expiration date	High	**Objective performance data:** Task Participants were asked to identify expiration date.	Must identify expiration date on safety syringe label.
Allow safety syringe to warm up before use	Low	**Subjective response data:** Knowledge probe Participants obtained a carton from the refrigerator for their unaided injection and were asked what should be done with the device before the injection.	Must state that they would let the device warm to room temperature for at least 30 minutes.
Drug product inspection	High	**Objective performance data:** Task Participants were asked to inspect the drug	Participant inspects drug through Inspection Window.
		Subjective response data:	

IFU Step	Risk Severity	Study Technique	Range of Acceptable Performance or Response
		Knowledge probe Participants were asked to identify if drug is good or degraded and state why. Feedback Participant commentary on any difficulty inspecting drug through the window.	Must know what good drug looks like (clear and colorless with no particles). N/A
Identification of injection site	High	**Subjective response data:** Knowledge probe Participants were asked to state the allowable injection sites before any pad is applied to their body.	Must respond abdomen and/or thigh.
Cleaning of injection site	Low	**Objective performance data:** Task Participants were observed regarding cleaning of the injection site.	Must clean injection site with alcohol swab.
Removal of needle cap	Medium	**Objective performance data:** Task Participants were observed regarding ability to remove the needle cap.	Must remove Needle Cap without injury and < 15[1] minutes before injection.
		Subjective response data: Feedback Participant commentary on any difficulty removing needle cap.	N/A
Pinch around injection site	Medium	**Objective performance data:** Task Participants were observed if they pinched around the injection site prior to needle insertion.	Attempt to pinch skin pad at the injection site.
Insertion of needle	High	**Objective performance data:** Task Participants were observed regarding proper needle insertion.	Needle is inserted at a slight angle (approximately 45º to injection surface) with most of the needle inserted into the skin pad.
		Subjective response data: Feedback Participant commentary on any difficulty inserting the needle.	N/A
Completion of injection	High	**Objective performance data:** Task Participants were observed regarding delivery of the full dose.	The entire dose must be dispensed (Plunger fully depressed) before removing the needle from the injection site.
		Subjective response data: Feedback Participant commentary on any difficulty completing the injection.	N/A
Syringe safety activation	Low	**Objective performance data:** Task Participants were observed regarding activation of the needle safety guard.	(b) (4)
		Subjective response data: Feedback Participant commentary on any difficulty activating the safety mechanism.	N/A
Safety syringe disposal	Medium	**Objective performance data:** Task Participants were observed regarding safety syringe disposal.	Must place used safety syringe into Sharps Container.

[1]Revised from submitted protocol based on needle tip drying study performed after submission.

6.3 Technique for Capturing Unanticipated Use Errors

All use errors which were not included in the risk analysis were documented. Testing staff was in close observation of the participant during the entire training and injection procedures in order to capture any unanticipated mal behaviors. In addition, recording equipment was utilized to capture any questionable behaviors and enable post-study video analysis. Participants were debriefed on any of these unanticipated use errors.

The following are potential user actions that are not part of normal use of the product and are not expected but may occur as anticipated via the risk assessment and human factors expert review. These are listed in the table below and were observed for occurrence during the study.

Unexpected Actions	Risk Severity	Clinical impact	Study Technique (Objective Performance Data)	Implemented Risk Mitigation
Pre-injection tampering	High	May result in needle stick to patient or other person in household, potential loss of dose, injection site infection or cross contamination.	Participants will be observed regarding tampering or interaction with the device.	Packaging will include tamper evident features.
Drops safety syringe	Low	May result in broken syringe (loss of drug or sterility) or accidental activation	Participants will be observed regarding instances of dropping the device before administering	Dedicated section in IFU with bold text and symbols stating the device should not be used if dropped. Drop testing conducted in
		of needle safety mechanism.	the injection. If the subject drops it, they will be observed regarding whether or not they continue to use that device.	accordance with ISO11608-1 demonstrating no impact on device performance or drug product quality
Shakes safety syringe	Medium	Shaking may impact to biologic product quality with unknown therapeutic consequences.	Participants will be observed regarding instances of shaking the device before administering the injection.	Dedicated section in IFU with bold text and symbols stating not to shake product. Shaking studies performed to demonstrate product is not sensitive to shaking.
Recaps safety syringe before injection	Low	May result in needle stick injury or damaged/bent needle causing painful injection.	Participants will be observed regarding instances of recapping the needle with the Needle Cap before administering the injection.	Dedicated section in IFU with bold text and symbols clearly stating for participant not to recap the device before injection.
Unintentional activation of needle safety mechanism during handling	Medium	Once the needle safety mechanism is actuated, the subject cannot inject any remaining dose in the syringe. User should be aware of failure and it is therefore correctable.	Participants will be observed regarding unintentional activation of device.	Device designed such that activation tabs are shielded to prevent unintended activation during handling.
Needle stick injury	Low	Needle stick injury with temporary patient discomfort or complaint.	Participants will be observed regarding needle stick injuries or close calls during the entire session.	Needle safety mechanism is designed to protect against unintentional needle access after use

C.2 Results

Summary of Results:

Autoinjector

Across both participant groups, all participants successfully administered the full dose during all of their unaided injections (45/45, 100%) without patterns of failures or use errors. Additionally, all participants (30/30, 100%) successfully answered all knowledge probe questions and identification tasks. One low risk unanticipated event of recapping the device was observed and discussed further below.

See the table below for all performance measures recorded during this study, organized by risk level.

8.1a Summary of Results – All Performance Measures

Observations/Measures	Risk	SLE Patients (N=15) 1 Injection	HCPs (N=15) 2 Injections	Overall (N=30)
Failure to identify usable drug through inspection	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to know how to identify good drug	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to identify expiration date	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to identify at least one allowable injection site	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to identify proper storage of autoinjector before use	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to know that drug should not be frozen	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to orient device approximately perpendicular to injection surface	High	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to activate the injection	High	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to deliver full dose	High	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to dispose of the device	Medium	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to remove the cap	Medium	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to identify the need to allow autoinjector to warm to room temperature	Low	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to identify ancillary supplies needed for injection	Low	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to remove device from blister pack	Low	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to open blister pack	Low	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to clean injection site	Low	0/15 (0%)	0/30 (0%)	0/45 (0%)
Unanticipated Events				
Recaps device before injection	Low	1/15 (7%)	0/30 (0%)	1/45 (2%)

Prefilled Syringe

Unaided Injection Trial Findings

Overall, all participants successfully administered all of their unaided injections (45/45, 100%) without patterns of failures or use errors. All participants (30/30, 100%) answered all knowledge probes without any difficulty. One medium-risk task failure for one SLE patient who did not pinch the injection site was observed across all participant critical and essential tasks.

See the table below for all performance measures recorded during this study, organized by risk level.

8.1a Summary of Results – All Performance Measures

Observations/Measures	Risk	SLE Patients (N=15) 1 Injection	HCPs (N=15) 2 Injections	Overall (N=30)
Failure to orient syringe at appropriate angle (approximately 45º)	High	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to deliver full dose	High	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to identify proper storage of syringe before use	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to know not to freeze syringe	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to identify usable drug through inspection	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to identify at least one allowable injection site	High	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to remove needle cap	Medium	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to pinch injection site	Medium	1/15 (7%)	0/30 (0%)	1/45 (2%)
Failure to activate needle safety guard	Medium	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to dispose of used syringe into sharps container	Medium	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to open blister pack	Low	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to remove syringe from blister pack	Low	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to clean injection site	Low	0/15 (0%)	0/30 (0%)	0/45 (0%)
Failure to identify ancillary supplies needed for injection	Low	0/15 (0%)	0/15 (0%)	0/30 (0%)
Failure to identify the need to allow safety syringe to warm to room temperature	Low	0/15 (0%)	0/15 (0%)	0/30 (0%)

APPENDIX D. ISMP NEWSLETTERS – N/A

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

APPENDIX F. OTHER – N/A

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,[h] along with postmarket medication error data, we reviewed the following Benlysta (b) (4) labels and labeling submitted by Human Genome Sciences, Inc. on September 22, 2016.

- Container label
- Carton labeling
- Instructions for Use

G.2 Label and Labeling Images

Container label

(b) (4)

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

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

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

/s/

MADHURI R PATEL
05/31/2017

MISHALE P MISTRY
05/31/2017

QUYNHNHU T NGUYEN
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