

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761058Orig1s000

OTHER REVIEW(S)

**GENERAL HOSPITAL DEVICES BRANCH
INTERCENTER CONSULT MEMORANDUM**

Date: 5/4/17

To: Sadaf Nabavian OMPT/CDER/OND/ODEII/DPARP

From: Matthew Ondeck CDRH/ODE/DAGRID/GHDB

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

Subject: Consult for BLA761058, ICC1700037 review memo

Applicant	Boehringer Ingelheim Pharmaceuticals
Indication for Use	Indicated for treatment of Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Ankylosing spondylitis, Psoriatic Arthritis, Psoriasis, Adult Crohn's disease and ulcerative colitis.
Drug / Biologic Constituent	BI 695501: Adalimumab
Device Constituent	Pre-filled syringe

Recommendation: The CDRH review team does not have any outstanding concerns and recommends that the device constituent parts of BLA76105 be approved.

Digital Signature Concurrence Table	
Reviewer	Matthew Ondeck -S 2017.05.04 21:51:26 -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=130 0189211, cn=Alan M. Stevens -S Date: 2017.05.04 22:23:17 -04'00'

I. Purpose / Background

BI submitted a BLA biosimilar to Humira for the same indications and DPARP would like to request for a consultative review of the device component data submitted by BI for the proposed pre-filled syringe presentation only; (b) (4)

The RPM stated that CDRH has not had any prior interactions on the BLA however there was CDRH involvement under IND110467. The meeting minutes from IND 110467 were reviewed and the sponsor has conducted container closure testing including microbial ingress until expiry and stability testing as requested as well as other CDRH concerns.

INSTRUCTIONS

The following instructions were provided to the consultant reviewer:

BI submitted a BLA biosimilar to Humira for the same indications and DPARP would like to request for a consultative review of the device component data submitted by BI for the proposed pre-filled syringe presentation only. This excludes any review of the drug substance.

Product	Indications for Use
BI 695501 in a pre-filled syringe	The following was taken from Ra00831699 In the US, BI 695501 is intended to be licensed for all approved non-exclusive indications of Humira, as follows: ☐ Rheumatoid Arthritis ☐ Juvenile Idiopathic Arthritis (4 years of age and older) ☐ Psoriatic Arthritis ☐ Ankylosing Spondylitis ☐ Adult Crohn's Disease ☐ Ulcerative Colitis ☐ Plaque Psoriasis

II. Administrative

Documents Reviewed:

Document Title	Document Number	Date -Version	Location
Description of the Container Closure System	q00233459-01	04 Jul 2016	GSR Sequence 0000(1) / Section 3.2.P.7 Pre-filled syringe – not specified
Breakloose and Extrusion Force	q00229166-01	12 August 2016	GSR Sequence 0000(1) / Section 3.2.P.5.3 Validation of Analytical Procedures
Specification	Q00228510-02	04 August 2016	GSR Sequence 0000(1)/ Section 3.2.P.5.1. Specification(s)
Accelerated and	q00235622-01	08 September	GSR Sequence 0000(1) / Section

Long-Term Stability Data		2016	3.2.P.8.3 Stability Data
Justification of Specification Functionality Testing	q00228515-01	15 August 2016	GSR Sequence 0000(1) / Section 3.2.P.5.6 Justification of Specifications
Draft label text IT7556aJ042016 clean orig BLA Word Version			GSR Sequence 0000(1) / Section 1.14.1.3. Draft labeling Text
Description and Composition of the Drug Product	q00231508-01	11 December 2015	GSR Sequence 0000(1) / Section 3.2.P.1 Description and Composition of the Drug Product
Introduction	Ra00831699	26 September 2016	GSR Sequence 0000(1) / Section 2.2 Introduction
Justification of Specification	q00228470-01	04 August 2016	GSR Sequence 0000(1) / Section 3.2.P.5.6
Justification of Specification Functionality Testing	q00228515-01	15 August 2016	GSR Sequence 0000(1) / Section 3.2.P.5.6
(b) (4)			
Risk Management Summary Report	q00240676-01	18 July 2016	GSR Sequence 0000(1) / Section 3.2.R Regional Info
Tabular listing of all Clinical Studies	c08846963-01	15 September 2016	GSR Sequence 0000(1) / Section 5.2
(b) (4)			
Design Validation Summary Report	q00242310-01	09 September 2016	GSR Sequence 0000(1) / Section 3.2.R Regional Info
List of Applied Standards	q00241451-02	16 August 2016	GSR Sequence 0000(1) / Section 3.2.R Regional Info
Risk Management Summary Report	Q00240676-01	18 June 2016	GSR Sequence 0000(1) / Section 3.2.R Regional Info
Post-Approval Stability Protocol and Stability Commitment	q00235619-02	01 August 2016	GSR Sequence 0000(1) / Section 3.2.P.8.2 Post Approval Stability Protocol and Stability Commitment
HFE_UE report attachment – prefilled syringe	Q00240985-01	02 August 2016	GSR Sequence 0000(1) / Section 5.3.5.4 hfe-ue- HFE/UE report – Prefilled syringe
HFE_UE report attachment – prefilled syringe	Q00240987-01	02 August 2016	GSR Sequence 0000(1) / Section 5.3.5.4 hfe-ue- HFE/UE report – Prefilled syringe
Justification of Specification	Q00228470-01	04 August 2016	GSR Sequence 0000(1) / Section 3.2.P.5.6 Justification of Specifications
Batch Analyses	q00228447-01	23 August 2016	GSR Sequence 0000(1) / Section 3.2.P.5.4 Batch Analyses
(b) (4) trade syringe label 40 mg/0.8 mL	N/A	N/A	GSR Sequence 0000(1) / Section 1.14.1.1 Draft Carton and Container Labels

Breakloose and Extrusion	Q00237308-01	16 June 2016	GSR Sequence 0000(1) / Section 3.2.R Regional Info
Extractable Volume	q00229118-01	07 June 2016	GSR Sequence 0000(1) / Section 3.2.P.5.2 Analytical Procedures

CDRH Review Team:

Team Member	Role	Deficiencies
Matthew Ondeck (CDRH/ODE/GHDB)	Lead Reviewer – Biomedical Engineer	#...

III. Device Description and Performance Requirements**Prefilled Syringe:**

The following was taken from the submission document: q00233459--1



The primary packaging of BI 695501 drug product (DP) consists of a 1 mL long pre-filled syringe (PFS) with a staked needle and rigid needle shield and is sealed with a (b) (4) plunger stopper. As shown in Figure 1, the PFS is assembled with an extended finger flange and a plunger rod to enable injection of the DP (ready-to-use). There is no contact between the finger flange and plunger rod and the DP solution. After the assembly process has been completed, the labeled PFS is placed in a blister pack.

Container/syringe is clear to allow for patient to view medication.



Figure 2 Representative technical drawing of the glass syringe



Table 1 Description of the syringe

Component	Details	Reference	Supplier
Glass barrel	1 mL long ready-to-fill glass barrel, (b) (4) glass type (b) (4) Type: (b) (4)	USP <660>	(b) (4)
	(b) (4) stainless steel 27G ½"	n.a.	
Rigid needle Shield	Inner Needle Shield: Rubber formulation (b) (4) contains latex Outer Rigid shield: (b) (4) (no product contact)	USP <381> n.a.	

The following images was taken from #q00240985-01. There is no graduation markings on the outside of the syringe. Because this is a single use and full dose injection, this may not be a problem. Graduation marks were removed from the container because of use error noticed with reading expiration date. (q00240986-01 pg118)

(b) (4)

After the summative study BI made a decision to remove the graduation marks of the PFS as the PFS contains preset single dose. That is, the PFS is a single use, disposable device. Graduation marks are used to measure dose and therefore this was considered to have been a possible safety related risk (also with observations in the first summative study) and they were removed.

The new PFS without the graduation marks was included in the supplemental summative study.

Instructions:

- **Cap:** The PFS's cap covers the needle and holds it in place. Removing the cap uncovers the PFS's needle.
- **Needle:** The PFS's needle is uncovered when the user removes the cap. Users insert the needle into the skin at about a 45° angle, after which users can press the plunger rod to inject medication.
- **Syringe barrel and medication:** The PFS's transparent barrel enables users to visually inspect (1) the medication (e.g., for clarity) before injecting, and (2) the plunger's position after injecting.
- **Plunger:** The rubber plunger creates a tight seal inside the syringe, preventing the drug from leaking out of the syringe's barrel and provides a sterility barrier. By pressing the plunger rod, the user must push the plunger down until all medication in the syringe has been delivered (i.e., until, the plunger reaches the bottom of the syringe).
- **Grip:** The grip is designed specifically to facilitate a more stable and secure grip for individuals with dexterity impairments. Users hold the grip when handling and injecting with the PFS.
- **Plunger rod:** Users should press the plunger rod to push the PFS's plunger down to inject medication into the body.

Device Characteristic	Description / Specification
Syringe Barrel Material Type	(b) (4) glass type (b) (4)
Needle Specifications • Length(s) • Gauge(s) • Connection type - o ISO 594 - o Prestaked	(b) (4) stainless steel 27 G ½ 12.7 mm (0.5 in) Same as A Prestaked needle
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	self-administration as well as administration by caregivers or health care providers
Residual Medication Volume	None
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	mL (syringe is 0.8 mL, single dose)
Storage conditions and expiry	Testing in progress, 2-8 °C up to 1 year (equivalent) Aiming for 2 year 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	Notes: No assembly No priming or dose steps Dispose after use. Clean with alcohol pad Do not inject through clothes Do not inject in bruised or scarred skin or within 1 in of a previous injection

through clothing, etc.)	Dispose after use
- Changing / disposing needles - Etc.	
Safety Features	Needle cap
Needle safety	
Breakloose Force	$\leq \begin{matrix} (b) \\ (4) \end{matrix} N$
Extrusion Force	$\leq \begin{matrix} (b) \\ (4) \end{matrix} N$

Reviewer Notes

There appears to be no info on the needle being bend resistant. This may not be an issue since the needle is single use only and has a cap and guard. Ask for info from sponsor.

This was addressed in an IR response from the sponsor. The sponsor states that this was taken into account in ISO 9296 testing specifications. This is no longer a concern.

IV. Design Control Review

The force specifications for the subject PFS are approximately 50% lower (as shown in Table 1) than those recommended by applicable medical device standards to accommodate the approximate 50% strength decrease in patients with RA. The specifications were also decreased by an additional 20% to account for females. The submission states that these parameters are according to ANSI/AAMI/ HE75: 2009 © 2013

The following was taken from q00228515-01

Table 1 Literature review on strength of RA patients in comparison to healthy people.

Reference No.	Handling force / grip of hand	Gender of proband	Strength RA patients afford in comparison to healthy people [%]
[1]	Hand grip	female	69
[2]	Hand grip strength	not discriminated	70
[3]	Maximum grip (N)	not discriminated	42
	Maximum pinch (N)	not discriminated	55
[4]	Grip strength right hand	female	56
	Grip strength left hand	female	55
[5]	Grip strength (N)	female	70
[6]	Key grip left	9 female, 1 male	42
	Key grip right	9 female, 1 male	33
[7]	Max. grip strength dominant hand	female	25
	Max. grip strength non-dominant hand		23
[8]	Max. isometric grip strength	not discriminated	73

Design Control Requirement	Acceptance Criteria Pre-Filled Syringe
Extractable Volume/Dose Accuracy	≥ 0.8 mL
Break-loose Force	$\leq$ (b) (4) N
Extrusion Force	$\leq$ (b) (4) N

Reasoning behind acceptance criteria

The following was taken from doc # q00228470-01: Justification of Specification

4.18.1 Specification for break-loose force

(b) (4)

Thus, the acceptance criterion for the maximum break-loose force for release and stability testing of BI 695501 DP is as follows:

Maximum break-loose force $\leq$ (b) (4) N

4.18.2 Specification for extrusion force

(b) (4)

Thus, the acceptance criterion for maximum extrusion force for release and stability testing of BI 695501 DP is as follows:

Maximum extrusion force $\leq$ (b) (4) N

The sponsor implements both a 50% decrease to account for the strength decrease in RA patients vs. healthy patients and an additional 20% to account for the difference between men and women.

Reviewer Note:

What is the acceptance criteria to remove the needle cap?

This was addressed in an IR response from the sponsor. The sponsor provided data for the needle cap removal force. The result of the needle cap removal force was tested 6 months accelerated storage, and it is well below the max force set by their acceptance criteria (b) (4) for patients with rheumatoid arthritis.

Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	
Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	Yes		3.2.P.5.1 Specification (Specs for PFS)
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	Yes		3.2..R Regional Info – Design Verification Reports
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	Yes		Risk Management Summary Report, 5.3.5.4 Hfe-ue-pfs -HFE_UE report attachment – Prefilled Syringe
Validation Data	Yes		5.3.5.4 Hfe-ue-pfs -HFE_UE report attachment – Prefilled Syringe 3.2.P.5.3 Validation of Analytical Procedures – Breakloose and Extrusion
Traceability Documentation	Yes		3.2R Design Verification Report (b) (4)

*Sponsor may derive the regulatory requirements from 21 CFR 820.30 into multiple sets of documents. For example, injectors containing software may include separate software requirements and specification documents. In these circumstances, additional rows may need to be added to the table.

A. Design Verification and Validation Review

Standard / Guidance		Conforms		
		Yes	No	N/A
Syringes	ISO 11040-4 Prefilled Syringes – Glass Barrel for Injectables	Yes		
	ISO 11040-5: Prefilled syringes - part 5: plunger stoppers for injectables.	Yes		
	ISO 7886, Sterile Hypodermic Syringes for Single Use;			N/A
Needle	ISO 7864, Sterile Hypodermic Needles for Single Use;			N/A

	ISO 9626, Stainless Steel Needle Tubing for Manufacture of Medical Devices;	Yes		
Sharps Injury Prevention Feature	Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features			N/A
	ISO 23908 - Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling			N/A
Connections	ISO 594-1: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: General Specifications			N/A
	ISO 594-2: Conical Fittings with 6% (Lure) Taper for Syringes, Needles and Certain Other Medical Equipment - Part 1: Lock Fittings			N/A

In the Design Verification Plan (Subsystem PFS) #q00241376-02; The sponsor states that they meet:

- ISO 9626, Stainless Steel Needle Tubing for Manufacture of Medical Devices;
- ISO 11040-4 Prefilled Syringes – Glass Barrel for Injectables
- ISO 11040-5: Prefilled syringes - part 5: plunger stoppers for injectables.
- FDA Guidance for Delivering Drug and Biological Products
- FDA Guidance for Container Closure Systems for Packaging Human Drugs and Biologics
- ISO 11608-3 PFS with Staked needles

Design Verification Review

Essential Performance Requirement	Specification	Verification Test Results (Y/N)	Shipping/Transportation (Y/N)	Lot Release Testing (Y/N)	Aging/Stability (Y/N)
Break Force	$\leq$ (b) (4) N	Yes	Yes	Yes	Yes
Glide Force	$\leq$ (b) (4) N	Yes	Yes	Yes	Yes
Expelled Volume	≥ 0.8 mL	Yes	No*	Yes	Yes
Tip Cap Removal	(b) (4) N	Yes	No*	Yes	Yes

* Note: The sponsor states that the sterile container closure/primary packaging was maintained during shipping (all passed). Therefore the needle cap removal force and expelled volume should not change after shipping. The reviewer agrees with this and this is response satisfactory.

Verification of Extrusion/Breakloose Force

The sponsor conducts testing to validate breakloose and extrusion force. They are able to show with multiple batches that they are below the pre-determined specifications. Doc #q00229166-01.

Lot release testing

The sponsor conducts functional testing of the PFS with different lots to verify the extrusion and breakloose force as well as the expelled volume across many different lots of PFS in doc #q00228447-01 pg. 11. All data meets design specifications.

Reviewer Note

There is no mention of tip cap removal force across different lots

This was addressed in an IR response from the sponsor. The sponsor provided data for the needle cap removal force. The result of the needle cap removal force was tested 6 months accelerated storage, and it is well below the max force set by their acceptance criteria (b) (4) for patients with rheumatoid arthritis. Although this data does not take into account validation after shipping, this data after accelerated aging will suffice. The data included in the IR from the sponsor is included below. The sponsor also states that this testing will be conducted to the 24 expiry and is ongoing.

Table 1 Results from design verification: RNS removal forces for pre-conditioning at 5°C ± 3°C

Sample No.	RNS removal force [N]		
	Initial analysis time point	3 months storage 25°C /60% RH	6 months storage 25°C /60% RH
1	7.37	6.73	7.32
2	8.40	7.73	8.75
3	8.96	7.41	8.78
4	10.40	10.75	9.08
5	10.30	9.60	7.80
6	7.90	7.86	8.88
7	10.19	9.68	8.69
8	8.92	8.47	8.62
9	8.77	11.19	9.66
10	10.32	6.96	8.74
11	12.56	7.67	8.37
12	9.71	7.85	8.42
13	9.74	10.73	8.75
14	8.75	9.85	8.31
15	10.51	9.82	8.65
Min	7.37	6.73	7.32
Max	12.56	11.19	9.66
Result	Pass	Pass	Pass

Aging/Storage Stability Verification

The reviewer notes that there is an accelerated aging plan with specifications for various analytical tests, however the reviewer cannot find aging up to 24 months which is the proposed shelf life.

At 5 deg C storage, breakloose and extrusion force and extractable volume of the PFS are verified to the predetermined specification up to 36 months of aging, with several lots tested

At 25 deg C accelerated aging storage, breakloose and extrusion force and extractable volume of the PFS are verified to the predetermined specification up to 12 months of aging, with limited lot testing

Shipping Verification

Reviewer Notes:

Please provide specs verification after shipping or transportation study of breakloose force, extrusion force, tip cap removal force, sharps prevention.

The sponsor provided functional data after a simulated shipping test according to ASTM 4169. The data revealed that the breakloose and extrusion forces were still within the respective

acceptance criteria. This is acceptable to the reviewer. The submission also stated that they are currently investigating real-time shipment validation which will be included in the annual report. This data is acceptable to the reviewer.

Blue Dye Ingress Test

Blue dye ingress testing was conducted to insure that the PFS container is indeed a sealed container. The container was sealed had no traces of blue dye and met the predetermined acceptance criteria.

Design Validation Review

Formative Evaluation 1

The sponsor conducted a formative evaluation study with 47 patients with RA, all of which used devices e.g. autoinjector pens or PFS for different RA medication. Patients were allowed to look at a non-functional AI (b) (4) and several things were taken from that and applied into the PFS, namely:

The following was taken from document #q00240985-01 pg 43

Finding related to autoinjector	Translation of design modification for the pre-filled syringe
RA patients considered the standard autoinjector model difficult to hold due to dexterity limitations	The PFS was equipped with an enlarged finger flange and an enlarged thumb rest for the plunger rod to facilitate a better grip, as compared to the standard syringe.
RA patients preferred slip-proof surfaces because their hands are commonly clammy (i.e., sweaty) when injecting (due to injection anxiety)	The enlarged finger flange and the thumb rest for the plunger rod was designed with a rough surface, to facilitate a better grip by textured surfaces.
RA patients preferred a large viewing window to ensure all medication was delivered	A transparent label was chosen for the PFS, in order to assure, that the user can easily identify when the plunger reached the end position of the PFS.
RA patients preferred bright, uplifting colors to enhance the emotional connection to the autoinjector	Apple green enlarged finger flange and white plunger rod was chosen as a positive and uplifting color for patients; commonly described as “fun and playful” or “brilliant and uplifting”; Green is also associated with positive feelings associated with being outdoors.

Formative Evaluation 2

A validation study using the PFS to test the usability of the PFS along with the IFU. This usability test was done using a placebo with the PFS, rather than the subject drug combo product The following was from document #q00240985

The submission states that the participants met all the evaluation objectives however they had some difficulty with the IFU, specifically:

- Waiting 30 min for medication to warm to room temperature
- Removing air from syringe

- Check to make sure no blood is in syringe to ensure that the user has not hit a blood vessel
- Squeezing skin after injection

The objectives of injecting the drug was met with the PFS. The above user issues are human factors/labeling related and are not a part of this review.

Formative Evaluation 3

A third evaluation/validation was done with 8 layperson participants with dexterity impairments, which the submission states is “worst case intended PFS users”, to administer an injection

Again there were several errors associated with administration, however they are not associated with the functionality of the device and are human factors related and will not be included in this review. Briefly, they included:

- Overlooking of disinfect the injection site
- Check to make sure no blood is in syringe to ensure that the user has not hit a blood vessel
- Too much information in IFU

Usability Study 1

A usability study involving 94 participants, RA patients, caregivers, and healthcare providers was conducted to test the PFS administration. Below is a table (taken from document q00240985-01 pg 77) of success rate involved with different tasks:

Function		Sub-tasks		No. of participants who performed the task	No. of participants who passed the task					
POF ID	Description				total	trained	untrained	experienced		inexperienced
									Sub group Humira experienced	
3	Inserting the needle into injection site	3.1	Clean injection site	94	89 of 94 (95%)	46 of 46 (100%)	43 of 48 (90%)	60 of 61 (98%)	14 of 14 (100%)	29 of 33 (88%)
		3.2	Choose appropriate injection site	94	91 of 94 (97%)	43 of 46 (93%)	48 of 48 (100%)	60 of 61 (98%)	14 of 14 (100%)	31 of 33 (94%)
		3.3	Place device at correct angle	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		3.4	Inject needle to correct depth	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		3.5	Push plunger down	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		3.6	Deliver complete dose	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		3.7	Verify complete dose	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
4	Removal of needle/device from injection site	4.1	Remove needle from skin	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
5	Disposal of device	5.1	Dispose of the device and safety cap in appropriate container	94	93 of 94 (99%)	46 of 46 (100%)	47 of 48 (98%)	60 of 61 (98%)	14 of 14 (100%)	33 of 33 (100%)

The reviewer notes that all user groups demonstrated that there were no issues with placing the needle at the correct angle, injecting the needle to the correct depth, pressing the plunger depth, delivering the full dose, and removing the needle from the skin, and capping appropriately.

Based on information received from users in the usability study and the formative evaluation, the sponsor implemented mitigation (largely augmenting or detailing the IFU). These all appear to be human factors with changes to the IFU, except for the removal of the graduation markings on the syringe. This was done to increase visibility of the expiration date and lot number.

The graduation markings are not necessary since this is a PFS and a single use syringe

Usability Study 2

A follow-up usability is done with several changes implemented from the first usability study. This was a study with 19 participants (RA patients, prospective caregivers and HCPs), split among experienced and inexperienced with injections. The following errors were reported from the study

Use error description	Number of participants who committed the use error
Did not check expiration date	10
Did not inspect PFS for cracks or damage	5
Did not check fluid clarity	5
User moved device position during injection	1
Did not inject into appropriate injection site	3
Recapped needle	2
Did not clean injection site	3
Did not discard used PFS in sharps container	1
Did not discard cap	1
Did not use PFS immediately after uncapping	1

Reviewer Note: 10 out of 19 participants did not check the expiration date. The sponsor may need to reword labeling to ensure that the patient sees this prior to injection. This is a human factors issue

5 participants did not inspect the PFS for cracks or damage. The sponsor may need to reword labeling to ensure that the patient sees this prior to injection. This is a human factors issue.

The only issue that is listed above that is a PFS issue is the “moved the device position during injection: The following was taken from q00240985-01

Use error description / participant-reported root causes

One participant tilted the needle after inserting it in the skin. Specifically, the participant inserted the needle at an angle of approximately 45°, and then tilted the PFS until it was almost perpendicular (i.e. making a 90° angle) to the injection cushion. After injecting all fluid, the participant tilted the PFS back to approximately 45° and removed the needle almost at the same angle as he inserted it.

The participant explained interpreting QGS Step 3's "Prepare Injection" illustration to instruct him to tilt the PFS 45° after inserting the needle into the skin and tilt it back before removing the needle from the skin. Specifically, the participant interpreted the illustration's black arrows indicating the 45° angle as an indication to tilt the PFS 45° after inserting and before removing the needle, rather than holding the PFS still at a 45° angle while administering the injection.

Reviewer Note

Although this could be determined to be a labeling/human factors issue as the participant states, the sponsor should look at bend/fracture resistance of the needle.

As recommended above the reviewer believes that the sponsor should supply bend/fracture resistance data on the needle to prevent a failure like this from occurring. Although this may be in the DMF.

This is not an issue. The sponsor states that this is a known issue with other syringes, however this did not occur with their syringe. Also the sponsor demonstrated that their needle complies with ISO 9626:1991 regarding needle bending. Therefore, this issue has been adequately addressed.

RISK MANAGEMENT

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	Yes		

The sponsor submitted a device related risk assessment in document q00240987-01. The majority of risk management tasks are labeling/human factors related since the PFS is a simple device; however the device portion focuses on the following:

- Device integrity
- Cap removal
- Inserting the needle into the correct site/angle
- User moves device during injection (see below for more thoughts)
- Incorrect dosing

Reviewer Note:

Missing hazards. Sponsor should address the following

- **Device fluid path occlusion**
- **Injection initiates prior to needle reaching the correct tissue depth of penetration**
- **Device contains sharp edges**
- **Needle bending**
- **Needle fragmentation**

These were implemented into the sponsor's risk analysis and any risk appears to be mitigated. The performance data supports the adequacy of the risk mitigation.

The sponsor receives their syringes from (b) (4) and included it into the risk management document.

3.2.1. EXTERNAL SUPPLIER

(b) (4)



B. Labeling

(b) (4)



Primary Package Labeling:

The sponsor plans to include 2 PFS's in each package. Each PFS is package in an individual blister tray with a sealed top. The following images are taken from document # q00240985-01

IFU:

(b) (4)



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

The Labeling is satisfactory from a CDRH standpoint

C. Design Transfer Activities – Release Specifications

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5:

Attribute	Specification	Test Method
Break Force	(b) (4) N	The breakloose and gliding forces are automatically measured using a calibrated material testing machine (Zwick). See below for detailed instructions
Glide Force	(b) (4) N	The breakloose and gliding forces are automatically measured using a calibrated material testing machine (Zwick). See below for detailed instructions
Dose Accuracy	≥0.8 mL	USP <697> 5 Syringes of BI695501 drug product are used for measurement.

Break and Glide Force-

The following was taken from document q00237308-01-

Procedure

The syringe is mounted in the test machine and the needle shield is carefully removed prior to measurement. The instrument starts accumulating data automatically when the load cell meets the plunger head. The plunger is then pushed through the syringe at a velocity of 304.8 mm/min for distance of 29 mm while the Force (in Newtons) is measured. The breakloose and extrusion forces are automatically determined as the maximum force observed from 0-2mm and 2-29 mm, respectively, and documented using data processing software. A total of 10 sample syringes are measured for each result.

Dose Accuracy-

The following was taken from document q00229118-01

Application

This method is intended to determine the extractable volume.

Description

The extractable volume is measured using the method described for “cartridges and prefilled syringes” in the monographs. Five syringes of BI 695501 drug product are used for the measurement. The volume of each syringe must comply with the specified value. The contents are reported in mL and calculated as the mass divided by the density of the solution.

V. Information Requests –

IR Sent 2/27/17

Can you ask the sponsor to provide the volume ID and the date of request for the DMF (b) (4) for the syringe components? I will need this for my review?

1. In the HFE/UE report a participant in the usability study moved the device and bent the needle while the injection was taking place, which is a needle fracture hazard. There is no information/data on the bend resistance of the needle in the submission. Provide information that successfully mitigates the risk of a bent needle resulting in a fracture hazard if (b) (4) dropped repeatedly.

Also, the Agency requests that you update your risk management report with the following risks and mitigations for each risk:

- Device fluid path occlusion
- (b) (4) component failure
- Injection initiates prior to needle reaching the correct tissue depth of penetration
- Device contains sharp edges
- Needle bending (included from above comment)
- Needle fragmentation

Sponsor Response

During the formative and summative Human Factor Studies carried out as part of the development of BI 695501 pre-filled syringe (PFS), no instances of bent needles were observed. The submission documentation (HFE/UE Report) contains an ‘Analysis of Known Problems’ including two reports on other products: in one case the device’s needle bent prior to use, and in the other case the user bent and re-straightened the device’s needle. Both of these entries in the ‘Analysis of Known Problems’ are related to insulin pens with changeable needles (i.e. not single-use, single entity combination products).

The BI 695501 PFS does not have a needle that is changeable, but a staked needle that is glued into the glass barrel of the syringe. In addition, the accompanying IFU instructs the user with relevant precautionary information. Specifically, the IFU requests the user not to use the device if the ‘PFS appears cracked, damaged, or leaking’.

The risks and mitigations with respect to ‘Device fluid path occlusion’ and ‘Device contains sharp edges’ have been added to the current Risk Analysis documentation. The respective Risk Management Report will be updated accordingly. The risk with respect to needle fragmentation is already recorded in the Risk Management documentation and mitigations are implemented.

The risks and associated mitigation regarding needle bending are also already documented. The 27G regular walled (RW) staked needle used is compliant with ISO 9626:1991 ‘*Stainless steel needle tubing for manufacture of medical devices*’. This ISO standard specifies dimensional and mechanical properties of stainless steel needle tubing. As such, the stiffness of a needle is ensured due to the specified maximum deflection values during bending. For a 27G RW needle, a maximum deflection of (b) (4) mm when applying a bending force of 5.5 N is specified. In addition, stainless steel needles compliant to ISO 9626:1991 fulfill the

requirements of the ‘resistance for breakage test’; for a RW stainless steel needle, the needle must not break during 20 cycles of bending back and forth at an angle of 25°.

Reviewer Response

The reviewer concurs that if the stainless steel needle meets the specifications of ISO 9626:1991 regarding needle bending, then this should not create an issue with the device. The sponsor also clarified that the bent needle mentioned in the HF study was not their product but was only an example of known problems.

The sponsor added “Device fluid path occlusion” and “device contains sharp edges” to their current Risk analysis documentation and add that their Risk Management Report will be updated accordingly. They also state that the needle fragmentation risk was already included in the Risk management document. Reviewer cannot locate it in the risk management file.

2. You refer to ASTM D4169 Packaging/Transport Validation in the risk management summary report; however you did not include any data to confirm the essential performance requirements of the pre-filled syringe after shipping. Provide data to demonstrate maintenance of the essential performance requirements after shipping.

Sponsor Response

The essential performance requirements are construed to refer to the intended functions of the BI 695501 pre-filled syringe (PFS), which have the potential to impact the safety or effectiveness of the product.

Boehringer Ingelheim (BI) does not use the term “Essential Performance” requirements (as defined in ISO 60601-1 (2013) ‘*Medical electrical equipment - Part 1: General requirements for basic safety and essential performance*’), but instead utilizes the term ‘Critical Quality Attributes’ (CQA) in accordance with ICH Q8 (2009). A CQA assessment has been carried out for the BI 695501 drug product. The CQAs identified are related to quantity, purity, safety and also functionality.

A study was performed to assess the potential impact on BI 695501 finished drug product quality (FDP, i.e. the packaged and labeled PFS) when exposed to the commercial shipping process (please also see Section 3.2.P.2 ‘Pharmaceutical Development’, Chapter 6.2, for further details). In this study, BI 695501 FDP was tested at simulated worst-case shipping conditions per industry standard method ASTM 4169, ‘*Standard Practice for Performance Testing of Shipping Containers and System*’. ASTM 4169 ‘distribution channel 2’ was chosen as it allows the user to create a test cycle if the transportation modes are well understood. As BI 695501 FDP will be shipped (b) (4) assurance level I was chosen as it is the most severe of the three levels (I, II, III) permitted in ASTM 4169. To simulate all of the potential shipping stresses to the product, a shipping profile was created. Five tests from ASTM 4169 were selected to mimic a typical shipment – (b) (4)

The testing profile is described in [Table 1](#).

Table 1 Test Profile for BI 695501 FDP

(b) (4)



The BI 695501 FDP from the study was analytically tested and evaluated against the BI 695501 DP release specifications valid at the time of analysis to confirm quality attributes, integrity and functionality were maintained. To determine product quality, the set of tests which are indicative of potential transportation stresses on the BI 695501 PFS were performed.

[Table 2](#) describes the drug product quality and functionality results for BI 695501 FDP.

Table 2 Results from Shipping Simulation Study – Product Quality, Safety and Functionality

CQA (Test Method)	Target Criteria	Results
<i>Product Quality Tests</i>		
Clarity and Degree of Opalescence	Clear to slightly opalescent (< Reference IV)	< Ref III
Appearance -Visible particles (Visual Inspection)	Solution essentially free from foreign particles, may contain few translucent, white to whitish product-related particles	no foreign or proteinaceous particles observed
Protein concentration (UV Scan)	(b) (4) mg/mL	49 mg/mL
Purity / Impurity (UP SEC)	(b) (4) % Aggregates (b) (4) % Monomer	Aggregates 1 % Monomer 99 %
Purity / Impurity (CEX HPLC)	APG (b) (4) % Main peak (b) (4) % BPG (b) (4) %	APG 16 % Main Peak 66 % BPG 18 %
Purity / Impurity (CGE reduced)	Sum of heavy and light chain: (b) (4) %	98 %
Purity / Impurity (CGE non-reduced)	Main peak: (b) (4) %	97 %
TNF alpha Binding (RLCA)	(b) (4) % of standard material	100 %
Sub-visible particles (light obscuration)	≥ 10 µm (b) (4) particles/syringe ≥ 25 µm (b) (4) particles/syringe	≥ 10 µm, 1569 particles/syringe ≥ 25 µm, 9 particles/syringe
<i>Safety Test (Integrity)</i>		
Container closure integrity (Blue dye ingress test)	CCI complies	pass
<i>Functionality Test</i>		
Break-loose and Extrusion	Report results	Break-loose: 6 N Extrusion: 5 N

The analytical results including functionality testing all met the pre-set target criteria and showed no detectable impact to BI 695501 FDP quality, safety (integrity) and functionality when exposed to the worst case shipping conditions including vibration, low pressure and mechanical shock testing.

In addition to the transport simulation study described above, real-time shipment validation studies of BI 695501 FDP (b) (4) are currently being conducted (b) (4) (please

see section P.3.5 ‘Process Validation- Transport Validation’ for further details). Currently eight shipments have been completed and samples are being collected for analysis.

The BI 695501 FDP testing includes container closure integrity test (CCIT) and break-loose and extrusion force testing. The results obtained will be documented and evaluated and will be reported in the first Annual Report for BI 695501.

Reviewer Response

The sponsor provided functional data after a simulated shipping test according to ASTM 4169. The data revealed that the breakloose and extrusion forces were still within the respective acceptance criteria. This is acceptable to the reviewer. The submission also stated that they are currently investigating real-time shipment validation which will be included in the annual report. This data is acceptable to the reviewer.

However, there is no note of expelled volume or needle cap removal force after shipping testing. Please provide this data and state whether each met their respective acceptance criteria

- 3. There is functional acceptance criteria for the breakloose and extrusion force of syringe to initiate injection stated in the submission; however, there is no mention of acceptance criteria specification to remove the needle cap from the syringe. Provide the specification of the force to remove the needle cap and whether this is verified through lot release testing, after shipping, and after aging/stability testing.**

The specification for the RNS (rigid needle shield; i.e. needle cap) removal force for the Boehringer Ingelheim (BI) BI 695501 pre-filled syringe (PFS) is set at (b) (4) N.

The lower limit (b) (4) ensures that the RNS remains correctly seated on the glass barrel of the syringe during processing and transportation and thus ensures container closure integrity as well as sterility of the PFS. The upper limit (b) (4) ensures usability of the PFS considering finger forces as described in ANSI /AAMI HE75:2009(R)2013 – ‘*Human Factors Engineering – Design of Medical Devices*’ and the capabilities of the user group (limited dexterity of patients with rheumatoid arthritis) and by applying additional safety margins. Agreed specifications between BI and the PFS manufacturer (b) (4) ensure that RNS removal forces of the bulk syringes delivered are within the above mentioned limits.

The RNS removal force was addressed during design verification (see Section 3.2.P.2 ‘Pharmaceutical Development’, Chapter 4.5.2). To ensure that this parameter is not adversely affected by different environmental conditions, pre-conditioning of the samples was carried out; this included storage for a minimum of 4 h at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$, at $23^{\circ}\text{C} \pm 5^{\circ}\text{C}/50\% \pm 25\% \text{ RH}$ and $40^{\circ}\text{C} \pm 2^{\circ}\text{C}/50\% \pm 10\% \text{ RH}$ respectively. Table 1 to Table 3 show the results obtained for the initial, as well as the 3 months and 6 months analysis time point after accelerated aging at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$. All obtained results complied with the pre-set specifications of (b) (4). The study is ongoing and will cover 24 months real-time storage at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$.

Table 1 Results from design verification: RNS removal forces for pre-conditioning at 5°C ± 3°C

Sample No.	RNS removal force [N]		
	Initial analysis time point	3 months storage 25°C /60% RH	6 months storage 25°C /60% RH
1	7.37	6.73	7.32
2	8.40	7.73	8.75
3	8.96	7.41	8.78
4	10.40	10.75	9.08
5	10.30	9.60	7.80
6	7.90	7.86	8.88
7	10.19	9.68	8.69
8	8.92	8.47	8.62
9	8.77	11.19	9.66
10	10.32	6.96	8.74
11	12.56	7.67	8.37
12	9.71	7.85	8.42
13	9.74	10.73	8.75
14	8.75	9.85	8.31
15	10.51	9.82	8.65
Min	7.37	6.73	7.32
Max	12.56	11.19	9.66
Result	Pass	Pass	Pass

Reviewer Response:

The sponsor provided data for the needle cap removal force. The result of the needle cap removal force was tested 6 months accelerated storage, and it is well below the max force set by their acceptance criteria (b) (4) for patients with rheumatoid arthritis. Although this data does not take into account validation after shipping, this data after accelerated aging will suffice.

IR Sent 3/3/17

4. Provide a declaration of conformance to the following FDA recognized standards

- ISO 7886-1 : Sterile hypodermic syringes for manual use
- ISO 7864: Sterile Hypodermic Needles for Single Use

Alternatively, please provide detailed information regarding the specifications of the needle in lieu of complying with the listed FDA recognized standards.

Sponsor Response

The FDA recognized standard ISO 7886-1 '*Sterile hypodermic syringes for manual use*' is classed as not applicable to the BI 695501 pre-filled syringe (PFS), as its scope explicitly excludes single-use syringes made from glass as well as syringes with staked needle. ISO 7886-1 is solely applicable to sterile single-use syringes for medical purposes made from plastic and does not contain any requirements for injection needles.

Hypodermic needles specified in the FDA recognized standard ISO 7864 '*Sterile Hypodermic Needles for Single Use*' are intended for use with syringes having a 6 % Luer conical fitting as specified in various ISO standards. This ISO standard is therefore in general also not applicable to the BI 695501 PFS with staked needle.

The 27 G regular wall (RW) needle used for the BI 695501 PFS is made from stainless steel according to ISO 9626 and has a length of ½ inch (12.7 mm) and a 5 bevel tip. The syringe barrel with staked needle (and rigid needle shield) (b) (4)

conforms to the FDA recognized standard ISO 11040-4 '*Prefilled syringes – Part 4: Glass barrels for injectable and sterilized subassembled syringe ready for filling*', Section 6.5.2 '*Needle*'.

- The tubing used to manufacture the stainless steel needle complies with ISO 9626 '*Stainless steel needle tubing for manufacture of medical devices*' regarding material and dimensions
- The bevel, dimensions and bonds on the staked needle syringe barrels follow ISO 7864 '*Sterile Hypodermic Needles for Single Use*'
- Needle length nominal value follows ISO 7864 '*Sterile Hypodermic Needles for Single Use*'
- The needles are lubricated (b) (4)
- The needle lumen patency value follows ISO 7864 '*Sterile Hypodermic Needles for Single Use*'
- Needle removal force is > 22 N in accordance with ISO 7864 '*Sterile Hypodermic Needles for Single Use*' requirements
- The needles are free from defects and particles as per ISO 7864 '*Sterile Hypodermic Needles for Single Use*' requirements

Reviewer Response

The sponsor is correct in stating that ISO 7886-1 is not applicable because the subject prefilled syringe is a glass syringe with a prestaked needle.

The sponsor is correct in stating that ISO 7864 is not applicable because the subject prefilled syringe with a prestaked needle, not a luer lock needle.

IR Sent 3/21/17

In response to the IR response, in file BLA761058 BI response- IR12_1March2017 Question 2

You provided functional data after shipping/transportation testing. However, expelled volume and needle cap removal force were not including in these results. Provide expelled volume and needle cap removal force

after shipping/transportation testing. Alternatively, provide a rationale for why expelled volume and needle cap removal force do not need to be included after shipping/transportation.

Sponsor Response:

Response:

The transport simulation study was performed to assess the potential impact on the BI 695501 pre-filled syringe (PFS) quality when exposed to the commercial shipping process. To determine product quality, only those tests that are indicative of potential transportation stresses were selected and tested. Both needle cap removal force and expelled volume were not tested following the transport simulation study. The rationale for this is as follows:

Needle Cap Removal Force:

The 1 mL-long glass barrel with staked needle and pre-mounted needle cap (i.e. RNS - rigid needle shield) is delivered (b) (4). The specification (b) (4) for the RNS removal force is set at (b) (4) Newtons.

(b) (4) this test was not considered indicative of potential transportation stresses such as mechanical handling and impact, vibration and low air pressure during the commercial shipping process. However, container closure integrity (CCI) of the PFS after the transport simulation was tested and demonstrated the integrity of BI 695501 in its primary packaging (n = 40, all results passed); this demonstrates that the RNS is still sitting solidly on the PFS after vibrational and mechanical shock, therefore fully maintaining the sterile barrier.

Expelled Volume:

Glass as used for the 1 mL-long glass barrel of the PFS, as well as the chosen rubber formulation of the plunger, were chosen (b) (4).

(b) (4) During commercial manufacture of every batch of BI 695501 PFS, extractable volume (i.e. expelled volume) is routinely tested as part of release testing prior to shipment of the batch. However, as part of the transport simulation study, extractable volume testing was not included, instead container closure integrity (CCI) testing was carried out.

CCI is indicative of potential transportation stresses that may cause leaks and must also be maintained to ensure product sterility.

CCI testing is also considered to be a surrogate for extractable volume testing for the purpose of estimating the impact of potential transportation stresses; if there are no leaks it can be assumed that the extractable volume is identical pre- and post-shipment. As CCI testing results met the pre-set acceptance criteria (n = 40, all results passed), it can therefore be concluded that extractable volume was also not impacted.

Reviewer Response:

Needle Cap Removal Force: The sponsor states that the sterile container closure/primary packaging was maintained during shipping (all passed). Therefore the needle cap removal force should not change after shipping. The reviewer agrees with this and this is response satisfactory.

Expelled Volume: The sponsor states that the sterile container closure/primary packaging was maintained during shipping (all passed). Therefore the expelled volume, which was validated before shipping, should not change after shipping. The reviewer agrees with this and this response is satisfactory.

VI. Outstanding Deficiencies

None

VII. Post-Market Commitments / Post-Market Requirements

The sponsor states that they will continue to test the essential design criteria in a real-time aging plan to the proposed expiry of 24 months.

VIII. Recommendation

The CDRH review team does not have any outstanding concerns and recommends that the device constituent parts of BLA76105 be approved.

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

/s/

SADAF NABAVIAN
08/29/2017



U.S. FOOD & DRUG
ADMINISTRATION

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

LABELS AND LABELING REVIEW

Date:	August 24, 2017
Reviewer:	Vicky Borders-Hemphill, PharmD Labeling Review Specialist Office of Biotechnology Products (OBP)
Through:	Richard Ledwidge, PhD, Product Quality Reviewer OBP/Division of Biotechnology Review and Research III
Application:	BLA 761058
Product:	Cyltezo (adalimumab-adbm)
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Date(s):	October 27, 2016, May 31, 2017, August 10, 2017, August 15, 2017, and August 23, 2017

I) RECOMMENDATION

The labels and labeling for Cyltezo (adalimumab-adbm) injection, 40 mg/0.8 mL single-dose prefilled syringe for subcutaneous use submitted on August 10, 2017 (prescribing information/medication guide/instructions for use), August 15, 2017 (container label and carton labeling), and August 23, 2017 (blister labeling) are acceptable from a quality perspective.

II) BACKGROUND AND SUMMARY DESCRIPTION

The Applicant, Boehringer Ingelheim Pharmaceuticals, Inc., submitted BLA 761058 for Cyltezo (adalimumab-adbm) on October 27, 2016 as a proposed biosimilar to US-licensed Humira (adalimumab; BLA 125057).

Table 1 presents relevant product information for adalimumab-adbm that the Applicant submitted on May 31, 2017, and US-licensed Humira (adalimumab).

Table 2. Relevant Product Information for biosimilar product and the US-licensed Humira		
Product Name	Biosimilar Product Name	US-licensed Humira
Proprietary Name:	Cyltezo	Humira
Nonproprietary Name:	adalimumab-adbm	adalimumab
Dosage Form:	Injection	Injection
Strength and Container-Closure:	40 mg/0.8 mL in a single-use prefilled glass syringe	80 mg/0.8 mL in a single-use prefilled pen and single-use prefilled glass syringe 40 mg/0.8 mL in a single-use

		prefilled pen, single-use prefilled glass syringe, and single-use glass vial for institutional use only 40 mg/0.4 mL in a single-use prefilled pen and a single-use prefilled glass syringe 20 mg/0.4 mL in a single-use prefilled glass syringe 20 mg/0.2 mL in a single-use prefilled glass syringe 10 mg/0.2 mL in a single-use prefilled glass syringe 10 mg/0.1 mL in a single-use prefilled glass syringe
Route of Administration:	subcutaneous	subcutaneous
Storage and Handling:	Must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, CYLTEZO may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. CYLTEZO should be discarded if not used within the 14-day period. Record the date when CYLTEZO is first removed from the refrigerator in the spaces provided on the carton and dose tray. Do not store CYLTEZO in extreme heat or cold.	Must be refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT FREEZE. Do not use if frozen even if it has been thawed. Store in original carton until time of administration to protect from light. If needed, for example when traveling, HUMIRA may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days, with protection from light. HUMIRA should be discarded if not used within the 14-day period. Record the date when HUMIRA is first removed from the refrigerator in the spaces provided on the carton and dose tray. Do not store HUMIRA in extreme heat or cold.
Indication:	• Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. • Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.	• Rheumatoid Arthritis (RA): Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. • Juvenile Idiopathic Arthritis (JIA): Reducing signs and symptoms of moderately to severely active polyarticular JIA in

	• Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. • Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS. • Adult Crohn's Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. • Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of CYLTEZO has not been established in patients who have lost response to or were intolerant to TNF blockers. • Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.	patients 4 years of age and older. • Psoriatic Arthritis (PsA): Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. • Ankylosing Spondylitis (AS): Reducing signs and symptoms in adult patients with active AS. • Adult Crohn's Disease (CD): Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab. • Pediatric Crohn's Disease: Reducing signs and symptoms and inducing and maintaining clinical remission in patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to corticosteroids or immunomodulators such as azathioprine, 6-mercaptopurine, or methotrexate. • Ulcerative Colitis (UC): Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of CYLTEZO has not been established in patients who have lost response to or were intolerant to TNF blockers. • Plaque Psoriasis (Ps): The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate. • Hidradenitis Suppurativa (HS): The treatment of moderate to severe hidradenitis suppurativa. • Uveitis (UV): The treatment of non-infectious intermediate, posterior and panuveitis in adult patients.
Dose and Frequency:	Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis: 40 mg every other week. (Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.)	Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis: 40 mg every other week. (Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg

	Juvenile Idiopathic Arthritis: ≥ 30 kg (66 lbs): 40 mg every other week Adult Crohn's Disease and Ulcerative Colitis: Initial dose (Day 1): 160 mg Second dose two weeks later (Day 15): 80 mg Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. <u>For patients with Ulcerative Colitis only:</u> Only continue CYLTEZO in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. Plaque Psoriasis: 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose.	every week.) Juvenile Idiopathic Arthritis: 10 kg (22 lbs) to <15 kg (33 lbs): 10 mg every other week 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week ≥ 30 kg (66 lbs): 40 mg every other week Adult Crohn's Disease and Ulcerative Colitis: Initial dose (Day 1): 160 mg Second dose two weeks later (Day 15): 80 mg Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. <u>For patients with Ulcerative Colitis only:</u> Only continue HUMIRA in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. Pediatric Crohn's Disease: 17 kg (37 lbs) to < 40 kg (88 lbs): Initial dose (Day 1): 80 mg Second dose two weeks later (Day 15): 40 mg Two weeks later (Day 29): Begin a maintenance dose of 20 mg every other week. ≥ 40 kg (88 lbs): Initial dose (Day 1): 160 mg Second dose two weeks later (Day 15): 80 mg Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. Plaque Psoriasis or Uveitis: 80 mg initial dose, followed by 40 mg every other week starting one week after initial dose. Hidradenitis Suppurativa: Initial dose (Day 1): 160 mg Second dose two weeks later (Day 15): 80 mg Third (Day 29) and subsequent doses: 40 mg every week.
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III) MATERIALS REVIEWED

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

Table 1: Materials Considered for this Label and Labeling Review

Materials Reviewed	Appendix Section
Proposed Labels and Labeling	A
Other	B (N/A)
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, patient labeling, instructions for use, container labels, and carton labeling for Cyltezo (adalimumab-adbm) injection, 40 mg/0.8 mL single-dose 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 [August 10, 2017 (prescribing information/medication guide/instructions for use), August 15, 2017 (container label and carton labeling), and August 23, 2017 (blister labeling) are acceptable (see Appendix D) from a quality perspective.

4 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 2: Label^{1,2} and Labeling³ Standards

Container⁴ Label Evaluation

Prefilled syringe label

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Proper Name</u> 21 CFR 610.60 21 CFR 201.50 21 CFR 201.10			x	considered a partial label
<u>Manufacturer name, address, and license number</u> 21 CFR 610.60			x	considered a partial label
<u>Lot number or other lot identification</u> 21 CFR 610.60 21 CFR 201.18 21 CFR 201.100			x	considered a partial label
<u>Expiration date</u> 21 CFR 610.60 21 CFR 201.17			x	considered a partial label
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.60			x	
<u>Statement: "Rx"</u>		x		considered a partial label

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	
<u>only</u> 21 CFR 610.60 21 CFR 201.100				
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24			x	considered a partial label
<u>No Package for container</u> 21 CFR 610.60			x	
<u>Partial label</u> 21 CFR 610.60 21 CFR 201.10		x		See DMEPA's review regarding the use of distinguishing suffix in the nonproprietary name.⁵ Include the dosage form "Injection" to appear underneath the proper name. Revise the licensed manufacturer and address to appear as the Applicant listed on the submitted Form FDA 356h per 21 CFR 610.60 (c) as follows: "Boehringer Ingelheim Pharmaceuticals, Inc." If space permits, add "US license No xxx" to appear underneath the licensed manufacturer name. <i>Applicant's revision is acceptable</i>
<u>No container label</u> 21 CFR 610.60			x	
<u>Visual inspection</u> 21 CFR 610.60			x	
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35			x	considered a partial label
<u>Route of administration</u> 21 CFR 201.5 21 CFR 201.100		x		If space permits, add the route of administration "For Subcutaneous Use Only" <i>Applicant's revision is acceptable</i>
<u>Preparation instructions</u> 21 CFR 201.5			x	

⁵ Mena-Grillasca CM. memorandum Nonproprietary Name Suffix review for Cyltezo (adalimumab-adbm) injection (BLA 761058). 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 18.

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
<u>Package type term</u> 21 CFR 201.5			x	considered a partial label
<u>Drugs</u> <u>Misleading</u> <u>statements</u> 21 CFR 201.6	x			
<u>Strength</u> 21 CFR 201.10 21CFR 201.100	x			
<u>Drugs</u> <u>Prominence of</u> <u>required label</u> <u>statements</u> 21 CFR 201.15	x			
<u>Spanish-language</u> <u>(Drugs)</u> 21 CFR 201.16			x	
<u>FD&C Yellow No. 5</u> <u>and/or FD&C</u> <u>Yellow No. 6</u> 21 CFR 201.20			x	
<u>Phenylalanine as a</u> <u>component of</u> <u>aspartame</u> 21 CFR 201.21			x	
<u>Sulfites; required</u> <u>warning statements</u> 21 CFR 201.22			x	
<u>Bar code label</u> <u>requirements</u> 21 CFR 201.25 21CFR 610.67		x		Ensure a linear barcode appears on the label and that there is sufficient white space so that it can be scanned per 21 CFR 610.67 <i>Applicant's revision is acceptable</i>
<u>Strategic National</u> <u>Stockpile</u> 21 CFR 610.68 21 CFR 201.26			x	
<u>Net quantity</u> 21 CFR 201.51	x			
<u>Usual dosage</u> <u>statement</u>			x	considered a partial label

Regulations	Conforms			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.55 21 CFR 201.100				
<u>Inactive ingredients</u> 21 CFR 201.100			x	considered a partial label
<u>Storage requirements</u>			x	considered a partial label
<u>Dispensing container</u> 21 CFR 201.100			x	

Package Label⁶ Evaluation

Prefilled syringe blister

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Proper name</u> 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10	x			Include the dosage form "Injection" to appear underneath the proper name. <i>Applicant's revision is acceptable</i>
<u>Manufacturer name, address, and license number</u> 21 CFR 610.61	x			
<u>Lot number or other lot identification</u> 21 CFR 610.61	x			
<u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17	x			
<u>Preservative</u> 21 CFR 610.61	x			
<u>Number of containers</u>			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	
21 CFR 610.61				
<u>Strength/volume</u> 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	x			
<u>Storage temperature</u> 21 CFR 610.61	x			Ensure that the dose tray includes storage requirements for storage at room temperature. Revise the storage information from "Store in refrigerator at 36°F to 46°F (2°C to 8°C) (b) (4)" to read "Store in refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. DO NOT FREEZE. If needed, you may store at room temperature to a maximum of 77°F (25°C) for up to 14 days in the original carton until time of use. Once stored at room temperature, do not place back in the refrigerator. Discard after 14 days. Write the date removed from the refrigerator ___/___/___." To accommodate this change, delete "Protect from light" and "Store in carton until time of use" since these will be included in the recommended storage statement above. <i>Applicant's revision is acceptable</i>
<u>Handling: "Shake Well", "Do not Freeze" or equivalent</u> 21 CFR 610.61	x			
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.61			x	
<u>Route of administration</u> 21 CFR 610.61 21 CFR 201.5	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 610.64				
<u>Bar code</u> 21 CFR 610.67 21 CFR 201.25		x		In revised version submitted via email 16Aug17, the applicant responded "The barcode was removed from the blister labeling component. The packaging material does not support consistent printing of a barcode, i.e., not technologically feasible to print on the packaging material". <i>Per § 201.25(c)(2), the bar code must appear on the drug's label. Section 321(k) of the Act defines "label," as follows: The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article; and a requirement made by or under authority of this chapter that any word, statement, or other information appear on the label shall not be considered to be complied with unless such word, statement, or other information also appears on the outside container or wrapper, if any there be, of the retail package of such article, or is easily legible through the outside container or wrapper".</i> <i>Additionally, § 201.25(c)(1)(ii) requires the bar code to remain intact under normal conditions of use.</i> <i>According to the definition of "label," if the bar code does not appear on the blister, it needs to be "easily legible through the outside container or wrapper." Is the bar code on the syringe easily legible through the blister labeling component at all times? If not, consider making modifications to assure the bar code on the prefilled syringe will be consistently and easily legible through the blister packaging or that it will appear on the blister labeling. Have you considered other approaches that would ensure that the bar code could be placed on the blister labeling, i.e. package redesign? Additionally, provide justification describing why it is not technologically feasible to consistently print on the packaging material of the blister labeling.</i> The Applicant responded: We have reevaluated the

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
				blister labeling and have moved content ("Rx only" moved to the top region of the label) and have added a linear barcode to the blister labeling. Additionally, it has been confirmed that the barcode on the prefilled syringe label is easily legible through the outside container similar to the Humira packaging. <i>The Applicant's revision and response are acceptable.</i>
<u>Strategic National Stockpile</u> 21 CFR 610.68 21 CFR 201.26			x	
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	x			
<u>Preparation instructions</u> 21 CFR 201.5	x			
<u>Package type term</u> 21 CFR 201.5	x			
<u>Drugs Misleading statements</u> 21 CFR 201.6	x			
<u>Drugs Prominence of required label statements</u> 21 CFR 201.15	x			
<u>Spanish-language (Drugs)</u> 21 CFR 201.16			x	
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20			x	
<u>Phenylalanine as a component of aspartame</u>			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.21				
<u>Sulfites; required warning statements</u> 21 CFR 201.22			x	
<u>Net quantity</u> 21 CFR 201.51	x			
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	x			
<u>Dispensing container</u> 21 CFR 201.100			x	
<u>Medication Guide</u> 21 CFR 610.60 21 CFR 208.24			x	see carton

Carton Labeling

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Proper name</u> 21 CFR 610.61 21 CFR 201.50 21 CFR 201.10	x			Include the dosage form "Injection" to appear underneath the proper name. <i>Applicant's revision is acceptable</i>
<u>Manufacturer name, address, and license number</u> 21CFR 610.61	x			
<u>Lot number or other lot identification</u> 21 CFR 610.61	x			
<u>Expiration date</u> 21 CFR 610.61 21 CFR 201.17	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Preservative</u> 21 CFR 610.61	x			
<u>Number of containers</u> 21 CFR 610.61	x			
<u>Strength/volume</u> 21 CFR 610.61 21 CFR 201.10 21 CFR 201.100	x			
<u>Storage temperature</u> 21 CFR 610.61		x		Ensure that the carton labeling includes storage requirements for storage at room temperature. Revise the storage information from "Store in refrigerator at 36°F to 46°F (2°C to 8°C) DO NOT FREEZE. Protect from light." to read "Store in refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. DO NOT FREEZE. If needed, you may store at room temperature to a maximum of 77°F (25°C) for up to 14 days in the original carton until time of use. Once stored at room temperature, do not place back in the refrigerator. Discard after 14 days. Write the date removed from the refrigerator ____/____/____." <i>Applicant's revision is acceptable</i>
<u>Handling: "Shake Well", "Do not Freeze" or equivalent</u> 21 CFR 610.61	x			
<u>Multiple dose containers (recommended individual dose)</u> 21 CFR 610.61			x	
<u>Route of administration</u> 21 CFR 610.61 21 CFR 201.5 21 CFR 201.100	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
<u>Known sensitizing substances</u> 21CFR 610.61	x			Statement provided "Needle cover for syringe contains dry natural rubber."
<u>Antibiotics added during manufacturing</u> 21 CFR 610.61			x	
<u>Inactive ingredients</u> 21 CFR 610.61 21 CFR 201.100	x			
<u>Adjuvant, if present</u> 21 CFR 610.61			x	
<u>Source of the product</u> 21 CFR 610.61			x	see PI
<u>Identity of each microorganism used in manufacturing</u> 21 CFR 610.61			x	see PI
<u>Minimum potency of product</u> 21 CFR 610.61	x			
<u>Rx only</u> 21CFR 610.61 21 CFR 201.100	x			
<u>Divided manufacturing</u> 21 CFR 610.63			x	
<u>Distributor</u> 21 CFR 610.64			x	
<u>Bar code</u> 21 CFR 610.67 21 CFR 201.25	x			
<u>Strategic National Stockpile</u> 21 CFR 610.68			x	

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
21 CFR 201.26				
<u>NDC numbers</u> 21 CFR 201.2 21 CFR 207.35	x			
<u>Preparation instructions</u> 21 CFR 201.5			x	
<u>Package type term</u> 21 CFR 201.5	x			
<u>Drugs</u> <u>Misleading statements</u> 21 CFR 201.6			x	
<u>Drugs</u> <u>Prominence of required label statements</u> 21 CFR 201.15	x			
<u>Spanish-language (Drugs)</u> 21 CFR 201.16			x	
<u>FD&C Yellow No. 5 and/or FD&C Yellow No. 6</u> 21 CFR 201.20			x	
<u>Phenylalanine as a component of aspartame</u> 21 CFR 201.21			x	
<u>Sulfites; required warning statements</u> 21 CFR 201.22			x	
<u>Net quantity</u> 21 CFR 201.51	x			
<u>Usual dosage statement</u> 21 CFR 201.55 21 CFR 201.100	x			

Regulations	Comply			Comments and Recommendations
	Yes	No	n/a	
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			
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		Add identifying characteristics per 21 CFR 201.57(c)(4). Injection: 40 mg/0.8 mL of CYLTEZO is a clear to slightly opalescent solution provided by a single-use, 1 mL prefilled glass syringe with a fixed 27 gauge, 1/2 inch needle and a gray inner needle cover. <i>Applicant revised as requested</i>
6.2 IMMUNOGENICITY		x		Recommendations include the following standard statement or appropriate modification at the beginning of the Immunogenicity subsection preceding the immunogenicity data (for biosimilar products see draft Guidance for Industry: Labeling for Biosimilar Products):

BEST
AVAILABLE
COPY

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				"As with all therapeutic proteins*, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to [insert product's nonproprietary name] in the studies described below with the incidence of antibodies in other studies or to other products may be misleading." <i>This recommendation was not included in the proposed revisions to the Applicant because TBBS and DPARP determined that the final paragraph for this section on immunogenicity conveys the above language. This ordering of information in the immunogenicity section is similar to the Amjevita PI.</i>
11 DESCRIPTION 21 CFR 201.57(c)(12)		x		Added in dosage form and identifying characteristics consistent with appearance specifications submitted to the BLA per 21 CFR 201.57(c)(12). List inactive ingredients in alphabetical order per USP <1091> Labeling of Inactive Ingredients. <i>Applicant revised as requested</i>
16 HOW SUPPLIED/ STORAGE AND HANDLING 21 CFR 201.57(c)(17)		x		Added in dosage form and identifying characteristics per 21 CFR 201.57(c)(17) <i>Applicant revised as requested</i>
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			
Ingredients		x		List inactive ingredients in alphabetical order per

Labeling Standards	Comply			Comments and Recommendations
	Yes	No	n/a	
				USP <1091> Labeling of Inactive Ingredients. <i>Applicant revised as requested</i>
Manufacturer Information 21 CFR 610.61, 21 CFR 610.64	x			

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



Vicky
Borders-Hemphill

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Richard
Ledwidge

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Date: 8/24/2017 02:08:25PM
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MEMORANDUM

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

DATE: August 24, 2017

TO: Badrul Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)
Office of New Drugs

FROM: Melkamu Getie-Kehtie, R.Ph., Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Addendum** to review of routine clinical inspections
conducted at Auckland Clinical Studies Limited,
Auckland, and Christchurch Clinical Studies Trust,
Christchurch, New Zealand for BLA 761058

Inspection summary

This is an addendum to the EIR review finalized on July 03, 2017. This addendum reviews an inspection conducted at SGS Belgium NV, Antwerpen, Belgium, which was pending at the time the original EIR review was finalized.

The Office of Study Integrity and Surveillance (OSIS) arranged for a clinical inspection of study 1297.8 (BLA 761058: BI 695501, a biosimilar to adalimumab) that was conducted at SGS Belgium NV, Antwerpen, Belgium.

No significant deficiencies were observed at the site and no Form FDA 483 was issued at the inspection closeout. The final inspection classification for this site is No Action Indicated (NAI).

After reviewing the inspectional findings, OSIS recommends accepting the clinical data from study 1297.8 for further FDA review.

Inspected study

Study Number: 1297.8

Study Title: Pharmacokinetics and safety of BI 695501 in healthy subjects: a randomized, double-blind, single-dose, parallel-arm, active-comparator clinical Phase 1 study

Dates of conduct: 02/04/2014-06/20/2014

Clinical site: SGS Belgium NV
Lange Beeldekensstraat 267
Antwerpen, Belgium

ORA investigator Lakecha N. Lewis audited the clinical portion of the above study at SGS Belgium NV, Antwerpen, Belgium between June 12 and June 16, 2017.

The inspection included a thorough examination of subject records, informed consent process, institutional review board approvals, test article accountability, adverse events, and case report forms. Reserve samples were collected from this site.

At the conclusion of the inspection, investigator Lakecha Lewis did not observe any objectionable findings and did not issue Form FDA 483 to the inspected clinical site. There were no discussion items for the inspection.

Conclusion

After reviewing the inspectional findings, OSIS concludes that the clinical data for SGS Belgium NV from the audited study (1297.8) are reliable. Therefore, OSIS recommends accepting the clinical data from study 1297.8 for further review.

Final Classification:

NAI

CC:

OTS/OSIS/Kassim/Choe/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au/Getie-Kehtie

Draft: MG 8/21/2017, 8/22/2017

Edit: SA 08/21/2017; SC 8/24/2017

Page 3 - Routine clinical inspection at SGS Belgium NV, Antwerpen, Belgium

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL SITES /SGS Belgium NV, Antwerpen, Belgium/BLA 761058_BI 695501 (proposed biosimilar to US-licensed Humira®)

OSI file #s: BE 7396

FACTS: 11719204

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

/s/

MELKAMU GETIE KEBTIE
08/24/2017

STANLEY AU
08/24/2017
Acting Team Lead

SEONGEUN CHO
08/24/2017

LABEL, LABELING, AND HUMAN FACTORS REVIEW

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

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

Date of This Review:	August 14, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761058
Product Name and Strength:	Cyltezo (adalimumab-adbm) 40 mg/0.8 mL Injection
Product Type:	Single-Ingredient Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Date:	October 27, 2016
OSE RCM #:	2016-2607 and 2016 2681
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Sarah K. Vee, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Associate Director (Acting):	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report, the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Cyltezo (adalimumab-adbm) injection (BLA 761058), in response to consults from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The Applicant submitted BLA 761058, a 351(k) application, on October 27, 2016 for a prefilled syringe containing Cyltezo (adalimumab-adbm), as a biosimilar to Humira.

2 MATERIALS REVIEWED

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

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

N/A=not applicable for this review

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Human Factors

The applicant conducted a HF Validation for the prefilled syringe (PFS) with Instructions for Use (IFU). Subsequently, the applicant decided to include a Quick Tips (QT) to the inner carton packaging and performed a second HF Validation focusing solely on the QT. This second study was not intended to evaluate revisions made to the IFU after the first study.

1. Study 1: HF Validation (PFS with IFU).

A total of 94 participants participated in the Human Factors validation studies. The study design included at least 15 trained participants and 15 untrained participants within each distinct user group (Rheumatoid Arthritis [RA] patients, caregivers, and healthcare providers [HCP]). Additionally, within the RA and caregiver user groups, at least 15 participants were injection naïve and 15 participants were injection experienced. The table below shows the breakdown of the study participants.

Distribution of participants across user groups and sub-groups

User Group	Trained			Untrained			Overall
	Injection-experienced	Injection-naïve	Total	Injection-experienced	Injection-naïve	Total	
RA patients	6	9	15	9	7	16	31
Prospective caregivers	7	8	15	9	8	17	32
HCPs	15	1	16	15	N / A	15	31
Overall	28	18	46	33	15	48	94

The methodology is identical to the protocol but is provided for context purposes. Each participant performed three trials. During the first and second trials, participants had the option to refer to the IFU or QT as needed. This approach was modeled after the expected real-world use scenario in which a user has access to, but might not use the IFU. During the third trial, the participant was required to closely follow the IFU or QT in order to validate the IFU or QT.

We note that all participants were able to perform the critical tasks associated with delivering the full dose (i.e. placing the PFS at the correct angle, inserting the needle, push plunger down, and deliver complete dose) correctly. The study reported several use errors occurring on non-critical tasks, which are tasks that do not prevent the patient from receiving the full dose. Nonetheless, the applicant made revisions to the IFU and to the PFS label. Our evaluation of the risks associated with the use of the Cyltezo PFS did not identify any new or unique risks for the proposed product. We agree with the applicant's revisions to the IFU. In addition, we agree with PLT recommendations to the IFU to enhance patient comprehension. As such, we do not have any additional recommendations at this time to further mitigate the observed errors.

2. Study 2: HF Validation for the Prefilled Syringe (PFS) with Quick Tips (QT).

A total of 19 participants participated in the Supplemental Human Factors validation studies. The study design included at 10 trained participants and 9 untrained participants within each distinct user group (Rheumatoid Arthritis [RA] patients, caregivers, and healthcare providers [HCP]). Additionally, within the RA and caregiver user groups, some participants were injection naïve and some were injection experienced.

Distribution of participants across user groups and sub-groups

User Group	Trained			Untrained			Overall
	Injection-experienced	Injection-naïve	Total	Injection-experienced	Injection-naïve	Total	
RA patients	2	1	3	2	1	3	6
Prospective caregivers	1	2	3	2	1	3	6
HCPs	4	N/A	4	3	N/A	3	7
Overall	7	3	10	7	2	9	19

Each participant performed three simulated injections during which they interacted with the PFS and its associated IFU and QT. After each injection, the test administrator conducted a post-task interview including open-ended questions regarding task performance.

We note that the type of use errors observed during the second HF validation were similar to those observed during the first HF validation study including: fail to check expiration date, fail to inspect PFS for cracks or damage, fail to check fluid for clarity, moved device during injection, wrong injection site, recapped needle, did not clean injection site, did not discard in sharps container, did not discard cap, did not use PFS immediately after uncapping. Our evaluation of these errors indicated that the use of the Quick Tips did not introduce any new or unique errors than those already observed with the IFU or with prefilled syringe devices. The applicant did not recommend further mitigations to the QT. (b) (4)

Therefore, we only have minor editorial recommendations for the QT based on Patient Labeling review of the IFU. We consulted with the Patient Labeling reviewer and she concurred with our recommendations to the QT.

Labels and Labeling

In addition to the HF validation studies, our review of the proposed IFU did not identify any additional concerns from a medication errors perspective. However, we provide recommendations to the Quick Tips to align them with the recommendations the Patient Labeling Team (PLT) provided to the IFU. These recommendations were shared and in agreement with the PL reviewer.

In addition, our review of the proposed container label, blister and carton labeling noted areas for improvement. We noted that the proper name is not at least half the size of the proprietary name on all instances where it is presented on the labels and labeling. The dosage form statement (i.e. injection) is not present on the labels and labeling. The package type 'single-use' is used throughout the labels and labeling instead of the correct term 'single-dose'. We defer to OPQ on the appropriate package type term. The container label should include a bar code and the route of administration statement. The labels and labeling should be revised to include the proposed, conditionally acceptable proprietary name Cyltezo and the conditionally acceptable proper name adalimumab-adbm.

Our recommendations to improve the container label, blister, carton, and Quick Tips labeling are provided in Section 4.1.

4 CONCLUSION & RECOMMENDATIONS

We find the Human Factors validation study results acceptable. Our review of the proposed container labels, blister and carton labeling identified areas for improvement. We provide recommendations for Boehringer Ingelheim in Section 4.1.

4.1 RECOMMENDATIONS FOR BOEHRINGER INGELHEIM PHARMACEUTICALS

A. General Recommendations (All labels and labeling)

1. Your proposed proprietary name Cyltezo was found conditionally acceptable. Therefore, revise the proprietary name from (b) (4) to read 'Cyltezo'.
2. Your proposed nonproprietary name suffix 'adbm' was found conditionally acceptable. Therefore, revise the proper name to read 'adalimumab-adbm'.
3. The proper name is not at least half the size of the proprietary name on all instances where it is presented on the labels and labeling. Ensure the proper name is at least half the size of the proprietary name on all instances where it is presented on the container labels and carton labeling in accordance with 21 CFR 201.10(g)(2).

4. Include the dosage form statement on a single line under the proper name. For example:

Cyltezo
(adalimumab-adbm)
Injection
40 mg/0.8 mL
 5. Revise the NDC placeholder XXXX-xxx to include the actual NDC numbers intended for your packaging configurations.
- B. Container Label
1. Consider removing the (b) (4) as it is prominently displayed on the label and it is non-sensical to healthcare providers and patients and may be confused for a lot number or NDC number. At a minimum, relocate to the bottom of the label and decrease the prominence by reducing the font size.
 2. Per 21 CFR 201.25(b)(2), include a bar code and ensure there is adequate white space around the linear bar code to facilitate scanning.
 3. Include the route of administration statement 'For subcutaneous use only'.
- C. Blister Labeling
1. Revise the Dosage statement to delete 'For single-use only'. This statement is already present on various places within the blister labeling and does not provide relevant dosing information.
- D. Carton Labeling (1 count; Sample)
1. Revise the statement 'Not for Sale' to read "Sample - Not for Sale".
 2. This carton contains one prefilled syringe. Therefore, the statement (b) (4) is not applicable and we recommend deleting.
- E. Quick Tips
1. (b) (4)
 - a. Revise header title to read 'Choose Injection Site'
 - b. Revise 1st bullet to read 'Choose an area on your upper thighs or belly, except for an area 2 inches around your belly button.'
 - c. Revise 2nd bullet to read 'Choose a different injection site each time you inject, at least 1 inch away from the previous injection site.'
 - d. Revise 3rd bullet to read 'Clean the injection site with an alcohol pad'.
 2. Inspect and Uncap
 - a. Revise 1st bullet to read 'Inspect the prefilled syringe....'
 - b. Revise 2nd bullet to read 'Pull the cap straight off the syringe. **Do Not** let the needle touch anything.' (please note that Do Not is presented in title case)
 - c. Revise 3rd bullet to read '**Do Not** recap the needle.' (please note that Do Not is presented in title case)
 3. Prepare Injection
 - a. Revise 1st bullet to read 'Squeeze the skin around the injection site and hold firmly.'
 - b. Revise 2nd bullet to read 'Hold the syringe at about a 45 degree angle to the injection site.'
 - c. Revise 3rd bullet to read 'Insert the needle into the injection site...'
 4. Administer Dose
 - a. Revise 1st bullet to read 'Slowly push the plunger down fully until the plunger reaches...'
 - b. Revise 2nd bullet to read 'Remove the needle from the injection site ...'

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Cyltezo that Boehringer Ingelheim submitted on October 27, 2016.

Table 2. Relevant Product Information for Cyltezo and the Reference Product		
Product Name	Cyltezo	US-licensed Humira
Initial Approval Date	N/A	January 31, 2002
Active Ingredient	Adalimumab-adbm	adalimumab
Indication	• Rheumatoid Arthritis (RA) • Juvenile Idiopathic Arthritis (JIA) in patients aged 4 years and older • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Adult Crohn's disease (CD) • Ulcerative Colitis (UC) • Plaque Psoriasis (Ps)	• Rheumatoid Arthritis (RA) • Juvenile Idiopathic Arthritis (JIA) • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Adult Crohn's disease (CD) • Pediatric Crohn's disease • Ulcerative Colitis (UC) • Plaque Psoriasis (Ps) • Hidradenitis Suppurativa (HS) • Uveitis (UV)
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection, solution	Injection, solution
Strength/How Supplied	40 mg/0.8 mL PFS	80 mg/0.8 mL Humira Pen 40 mg/0.8 mL Humira Pen 40 mg/0.4 mL Humira Pen 80 mg/0.8 mL PFS 40 mg/0.8 mL PFS 40 mg/0.4 mL PFS 20 mg/0.4 mL PFS 20 mg/0.2 mL PFS 10 mg/0.2 mL PFS 10 mg/0.1 mL PFS 40 mg/0.8 mL vial for institutional use only
Dose and Frequency	Cyltezo is administered by subcutaneous injection. • Adult RA 40 mg every week or every other week • Adult PsA, and AS 40 mg every other week • JIA ≥ 30 kg: 40 mg every other week	Humira is administered by subcutaneous injection. • Adult RA 40 mg every week or every other week • Adult PsA, and AS 40 mg every other week • JIA 10 kg to < 15 kg: 10 mg every other week

	• Adult Crohn's disease and Ulcerative Colitis Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week • Adult Ps Initial dose: 80 mg Then: 40 mg every other week starting one week after initial dose	15 kg to < 30 kg: 20 mg every other week ≥ 30 kg: 40 mg every other week • Adult Crohn's disease and Ulcerative Colitis Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week • Pediatric Crohn's disease 17 kg to < 40 kg: Day 1: 80 mg Day 15: 40 mg Day 29: 20 mg every other week ≥ 40 kg: Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every other week • Adult Ps or Uveitis Initial dose: 80 mg Then: 40 mg every other week starting one week after initial dose • Adult HS Day 1: 160 mg Day 15: 80 mg Day 29: 40 mg every week
Storage	Refrigerated at 36° to 46°F (2° to 8°C). If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days.	Refrigerated at 36° to 46°F (2° to 8°C). If needed, may be stored at room temperature up to a maximum of 77°F (25°C) for a period of up to 14 days.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On July 2, 2017 we searched DMEPA's previous reviews using the term "adalimumab". Our search identified three previous relevant reviews, and we confirmed that our previous recommendations were implemented or considered.

McMillan, T. Human Factors Protocol Review for Biosimilar to Adalimumab (IND110467). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 May 29. RCM No.: 2013-1133
McMillan, T. Human Factors, Label, and Labeling Review for Biosimilar to Adalimumab (IND110467). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 Sep 23. RCM No.: 2013-2474
McMillan, T. Human Factors Protocol Review for Biosimilar to Adalimumab (IND110467). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 May 28. RCM No.: 2014-927

APPENDIX C. HUMAN FACTORS STUDY

HF VALIDATION PFS WITH IFU

8.7 SUMMATIVE USABILITY STUDY PART 1

8.7.1 Number and type of test participants

The summative usability test included 94 participants from three distinct user groups: RA patients, prospective caregivers, and HCPs. Half of each distinct user group received training, and the other half did not. [Table 23](#) presents the number of participants from each distinct user group by training status and injection experience. [Table 24](#) summarizes additional participant demographic background data and Humira experience.

The test included at least 15 trained participants and 15 untrained participants within each distinct user group (RA patients, caregivers, and HCPs), thereby matching FDA's expectations as indicated in the agency's feedback on the original summative test plan that BI submitted for review. Additionally, within the RA patient and caregiver user groups, at least 15 participants were injection-naïve and at least 15 participants were injection experienced. The 94-participant test included the following individuals:

Table 23 Distribution of participants across user groups and sub-groups

User Group	Trained			Untrained			Overall
	Injection-experienced	Injection-naïve	Total	Injection-experienced	Injection-naïve	Total	
RA patients	6	9	15	9	7	16	31
Prospective caregivers	7	8	15	9	8	17	32
HCPs	15	1	16	15	N / A	15	31
Overall	28	18	46	33	15	48	94

Table 24 Additional participant demographic data and relevant experience

Characteristic	Data by user group		
	RA patients	Prospective caregivers	HCPs
Age	Range = 25 – 73, Average = 52.4	Range = 22 – 62, Average = 44.2	Range = 35 – 69, Average = 49.7
Sex	Male = 8, Female = 23	Male = 11, Female = 21	Male = 15, Female = 16
Highest education level completed	High school / GED = 6 Some college = 4 College = 18 Advanced degree = 3	High school / GED = 2 Some college = 12 College = 11 Advanced degree = 7	N / A; all college or higher level
Current Humira experienced	7	1	6

8.7.2 Test participant training

46 out of 94 participants (48.9%) received 15-30 minutes of training from an independent nurse educator with injection training experience. This nurse, who was not affiliated with BI, was contracted by (b) (4) to deliver the training to the test participants.

The nurse was a Certified Diabetes Educator (CDE). Each trained RA patient, lay caregiver, and HCP received one-on-one training. During training, each participant was oriented to the PFS and its associated IFU, received a demonstration from the nurse trainer, and then “return demonstrated” a simulated injection into the injection cushion provided. The trainer intervened when necessary during the return demonstration to ensure that the participant performed all steps correctly, just as she would in a real training session. The training provided during the summative test closely matched the training BI expects actual end users to receive when the device is placed in actual use.

Trained participants’ test sessions occurred at least two hours and up to four days after the associated training sessions. This training delay properly simulated the real-world use

scenario, in which users would likely inject the first dose a few hours or days after receiving training and after picking up the PFS from the pharmacy. Participants did not have access to the PFS or the IFU during the period following training and up until the test session. As such, participants could not prepare for the test beyond participating in their training session (i.e., there was no opportunity to study or refresh on the product details).

Summary of Results

The following table summarizes the use-errors observed:

Use-Error	Number of Participants that Committed the Error ¹	Total Number of Use-Errors Observed
Fail to check for damages, cracks or leakage	31	75
Fail to check for drug appearance	25	57
Wrong injection site	28	54
Recapping needle	1	3
Fail to check expiration date	17	34
Fail to clean injection site	11	15
Discard device improperly	5	14

¹ Total number of participants = 94

² Total number of trials = 282

These are considered non-critical tasks as they do not prevent the patient from receiving the full dose and would not typically cause serious harm.

Nonetheless, the applicant's root cause analysis and risk assessment resulted in additional risk mitigation.

Use-Error	Root Cause Analysis/ Risk Assessment	Risk Mitigation
Fail to check for damages, cracks or leakage	Expectation that damage would be evident. Reliance on IFU. IFU Step 2 length. Trained users committed substantially fewer errors. Errors decreased in 2 nd and 3 rd trial. Drug loss/decrease effectiveness.	IFU revision to clarify Step 2 First bullet point to read 'Inspect prefilled syringe, medication, and expiration date' and 'Do Not use if: Prefilled syringe appears cracked, damaged, or leaking'.
Fail to check for drug appearance	Expectation that any discoloration would be evident. Reliance on IFU. IFU Step 2 length. Negative transfer. Test artifact. Trained users committed substantially fewer errors. Errors decreased in 2 nd and 3 rd trial. Use of degraded drug/decrease effectiveness.	IFU revision to clarify Step 2 First bullet point to read 'Inspect prefilled syringe, medication, and expiration date'
Wrong injection site	Reliance on IFU. Negative transfer. Perceived importance (i.e. assuming the injection site would heal within 2 weeks). IFU Step 5 presentation. Test artifact. Intramuscular injection/modified PK profile.	None
Recapping needle	Exposed needle after use. Negative transfer. Perceived safety in recapping. Habit. Trained users committed substantially fewer errors. Errors decreased in 2 nd and 3 rd trial. Needle stick.	IFU revision to add Step 7 'Do Not attempt to recap the needle.'

Use-Error	Root Cause Analysis/ Risk Assessment	Risk Mitigation
Fail to check expiration date	Reliance on IFU. Expiration date format. Perceived responsibility. Test artifact. Use expired drug/decreased effectiveness.	Increasing the prominence of the expiration date (font size and bold) on the PFS label. Changing the label orientation by 180 degrees. IFU revision to clarify Step 2 First bullet point to read 'Inspect prefilled syringe, medication, and expiration date'
Fail to clean injection site	Reliance on IFU. IFU's folded format. Negative transfer. Forgetfulness. Planned distraction. Test artifact. Trained users committed substantially fewer errors. Errors decreased in 2 nd and 3 rd trial. Contamination/infection.	None.
Discard device improperly	Negative transfer. Unfamiliarity with sharps container. Needle stick.	None.

Detailed Results

Table 26 Performance success rates

POF ID	Function Description	Sub-tasks		No. of participants who performed the task	No. of participants who passed the task					
					total	trained	untrained	experienced		inexperienced
									Sub group Humira experienced	
1	Safe transport and storage by user	1.1	Box handling	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		1.2	Box integrity	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		1.3	Box opening	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		1.4	Blister integrity	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		1.5	Blister opening	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		1.6	IFU reading	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		1.7	Removing the device from packaging	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)

Table 26 (cont'd) Performance rates

Function		Sub-tasks		No. of participants who performed the task	No. of participants who passed the task					
POF ID	Description				total	trained	untrained	experienced		inexperienced
									Sub group Humira experienced	
2	Preparation and inspection of drug/device	2.1	Check Drug integrity (color/appearance)	94	77 of 94 (82%)	45 of 46 (98%)	32 of 48 (67%)	51 of 61 (84%)	12 of 14 (86%)	26 of 33 (79%)
		2.2	Check expiration date	94	87 of 94 (93%)	46 of 46 (100%)	41 of 48 (85%)	58 of 61 (95%)	14 of 14 (100%)	29 of 33 (88%)
		2.3	Check drug dose	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		2.4	Check Device integrity	94	68 of 94 (72%)	44 of 46 (96%)	24 of 48 (50%)	47 of 61 (77%)	10 of 14 (71%)	21 of 33 (64%)
		2.5	Bring drug/device to room temperature	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		2.6	Remove cap	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)

Table 26 (cont'd) Performance success rates

Function		Sub-tasks		No. of participants who performed the task	No. of participants who passed the task					
POF ID	Description				total	trained	untrained	experienced		inexperienced
									Sub group Humira experienced	
3	Inserting the needle into injection site	3.1	Clean injection site	94	89 of 94 (95%)	46 of 46 (100%)	43 of 48 (90%)	60 of 61 (98%)	14 of 14 (100%)	29 of 33 (88%)
		3.2	Choose appropriate injection site	94	91 of 94 (97%)	43 of 46 (93%)	48 of 48 (100%)	60 of 61 (98%)	14 of 14 (100%)	31 of 33 (94%)
		3.3	Place device at correct angle	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		3.4	Inject needle to correct depth	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		3.5	Push plunger down	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		3.6	Deliver complete dose	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
		3.7	Verify complete dose	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
4	Removal of needle/device from injection site	4.1	Remove needle from skin	94	94 of 94 (100%)	46 of 46 (100%)	48 of 48 (100%)	61 of 61 (100%)	14 of 14 (100%)	33 of 33 (100%)
5	Disposal of device	5.1	Dispose of the device and safety cap in appropriate container	94	93 of 94 (99%)	46 of 46 (100%)	47 of 48 (98%)	60 of 61 (98%)	14 of 14 (100%)	33 of 33 (100%)

Table 27 Overall use error summary

Use error description	Number of participants who committed use error	Total number of use errors committed	Risk Identifier associated with the use error
User does not check for damages, cracks or leakage and risks use of damaged device.	26 (10 P, 2 PT, 9 C, 5 H)	62 (24 P, 5 PT, 20 C, 12 H)	<i>POF2.2.4.13</i> <i>POF 2: Preparation and inspection of drug/device</i>
	<i>Humira experienced users: 4 (4 P)</i>	<i>by Humira experienced users: 9</i>	<i>Sub task 2.4: Check Device integrity</i> <i>Potential Use error 13: User does not check for damages, cracks or leakage and risks use of damaged device.</i>
User does not check for drug appearance (cloudy, discolored, frozen,	17 (5 P, 1 PT, 8 C, 3 H)	38 (11 P, 2 PT, 18 C, 7 H)	<i>POF2.2.1.10</i> <i>POF 2: Preparation and inspection of drug/device</i>
	<i>Humira experienced users: 2 (2 P)</i>	<i>by Humira experienced users: 3 (3 P)</i>	<i>Sub task 2.1: Check Drug integrity (color/appearance)</i> <i>Potential Use error 10: User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles)</i>
User selects inappropriate or wrong injection site	3 (3 PT)	6 (6 PT)	<i>POF3.3.2.32</i>
	<i>Humira experienced users: 0</i>	<i>by Humira experienced users: n/a</i>	<i>POF 3: Inserting the needle into injections site</i> <i>Sub task 3.2: Choose appropriate injection site</i> <i>Potential Use error 32: User selects inappropriate or wrong injection site</i>
User recaps needle	1 (1 P)	3 (3 P)	<i>POF5.5.1.46</i>
	<i>Humira experienced users: 0</i>	<i>by Humira experienced users: n/a</i>	<i>POF 5: Disposal of device</i> <i>Sub task 5.1: Dispose of the device and safety cap in appropriate container</i> <i>Potential Use error 46: User recaps needle</i>

Table 27 (cont'd) Overall use error summary

Use error description	Number of participants who committed use error	Total number of use errors committed	Risk Identifier associated with the use error
User does not check expiration date	7 (7 C) <i>Humira experienced users: 0</i>	14 (14 C) <i>by Humira experienced users: n/a</i>	<i>POF2.2.2.12</i> <i>POF 2: Preparation and inspection of drug/device</i> <i>Sub task 2.2: Check expiration date</i> <i>Potential Use error 12: User does not check expiration date</i>
User does not clean injection site	5 (1 P, 4 C) <i>Humira experienced users: 0</i>	7 (1 P, 6 C) <i>by Humira experienced users: n/a</i>	<i>POF3.3.1.17</i> <i>POF 3: Inserting the needle into injections site</i> <i>Sub task 3.1: Clean injection site</i> <i>Potential Use error 17: User does not clean injection site</i>
User discards device in an improper way	0 <i>Humira experienced users: 0</i>	0 <i>by Humira experienced users: n/a</i>	<i>POF5.5.1.44</i> <i>POF 5: Disposal of device</i> <i>Sub task 5.1: Dispose of the device and safety cap in appropriate container</i> <i>Potential Use error 44: User discards device in an improper way</i>

Table 28 Concluding Results - User does not check for damages, cracks or leakage and risks use of damaged device

	Concluding Results
Description	User does not check for damages, cracks or leakage and risks use of damaged device
Number of participants who committed the use error	Total: 26 (10 P, 2 PT, 9 C, 6 H) Humira experienced users: 4 of 14 (4 P)
Total number of use errors committed	Total: 62 (24 P, 5 PT, 20 C, 12 H) By Humira experienced users: 9 (9 P)
Possible root causes	Expected visibility of PFS damage, Reliance on IFU, IFU Step 2's length
Risk(s) associated with Use error	<i>POF 2: Preparation and inspection of drug/device</i> <i>Sub task 2.4: Check Device integrity</i> <i>Potential Use error 13: User does not check for damages, cracks or leakage and risks use of damaged device</i> The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 29 Concluding Results - User does not check for drug appearance

	Concluding Results
Description	User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles)
Number of participants who committed the use error	Total: 17 (5 P, 1 PT, 8 C, 3 H) Humira experienced users: 2 (2 P)
Total number of use errors committed	Total: 38 (11 P, 2 PT, 18 C, 7 H) By Humira experienced users: 3 (3 P)
Possible root causes	Expected visibility of unsuitable fluid, Reliance on IFU (due to unintuitive step), IFU Step 2's length
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.1: Check Drug integrity (color/appearance) Potential Use error 10: User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles) The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 30 Concluding Results - User selects inappropriate or wrong injection site

	Concluding results
Description	User selects inappropriate or wrong injection site
Number of participants who committed the use error	Total: 3 (3 PT) Humira experienced users: none
Total number of use errors committed	Total: 6 (6 PT) By Humira experienced users: n/a
Possible root causes	Reliance on IFU (due to unintuitive step), IFU Step 5 text presentation
Risk(s) associated with Use error	POF 3: Inserting the needle into injections site Sub task 3.2: Choose appropriate injection site Potential Use error 32: User selects inappropriate or wrong injection site The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 31

Concluding results - User recaps needle

	Concluding Results
Description	User recaps needle
Number of participants who committed the use error	Total: 1 (1 P) Humira experienced users: none
Total number of use errors committed	Total: 3 (3 P) By Humira experienced users: n/a
Possible root causes	Exposed needle after use
Risk(s) associated with Use error	POF 5: Disposal of device Sub task 5.1: Dispose of the device and safety cap in appropriate container Potential Use error 46: User recaps needle The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 32

Concluding results - User does not check expiration date

	Concluding Results
Description	User does not check expiration date
Number of participants who committed the use error	Total: 7 (7 C) Humira experienced users: none
Total number of use errors committed	Total 14 (14 C) By Humira experienced users: n/a
Possible root causes	Reliance on IFU (due to unintuitive step) Expiration date format
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.2: Check expiration date Potential Use error 12: User does not check expiration date The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 33 Concluding results - User does not clean injection site

	Concluding Results
Description	User does not clean injection site
Number of participants who committed the use error	Total: 5 (1 P, 4 C) Humira experienced users: none
Total number of use errors committed	Total: 7 (1 P, 6 C) By Humira experienced users: n/a
Possible root causes	Reliance on IFU (due to unintuitive step) IFU's folded format
Risk(s) associated with Use error	POF 3: Inserting the needle into injections site Sub task 3.1: Clean injection site Potential Use error 17: User does not clean injection site The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 34 Concluding results - User discards device in an improper way

	Concluding Results
Description	User discards device in an improper way
Number of participants who committed the use error	Total: 0 Humira experienced users: none
Total number of use errors committed	Total: 0 By Humira experienced users: n/a
Possible root causes	None
Risk(s) associated with Use error	POF 5: Disposal of device Sub task 5.1: Dispose of the device and safety cap in appropriate container Potential Use error 44: User discards device in an improper way The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 35

Close call summary

Close call description	Number of participants who encountered the close call	Total number of close calls encountered	Risk Identifier associated with the close call
Almost did not inject appropriate injection site	3 (1 PT, 1 C, 1 HT)	3 (1 PT, 1 C, 1 HT)	<i>POF3.3.2.32</i> <i>POF 3: Inserting the needle into injections site</i> <i>Sub task 3.2: Choose appropriate injection site</i> <i>Potential Use error 32: User selects inappropriate or wrong injection site</i>
Almost injected with contaminated needle	1 (1 C)	1 (1 C)	<i>POF2.2.6.30</i> <i>POF 2: Preparation and inspection of drug/device</i> <i>Sub task 2.6: Remove cap</i> <i>Potential Use error 30: User does not use device immediately when cap/RNS is removed</i>
Almost did not store PFS in refrigerator	1 (1 C)	1 (1 C)	<i>POF1.1.1.01</i> <i>POF 1: Safe transport and storage by user</i> <i>Sub task 1.1: Box handling</i> <i>Potential Use error 01: User does transport or store device in improper way</i>
Inspecting fluid contained within the PFS and calls service number for support	6 (2 P, 1 PT, 1 C, 2 CT)	6 (2 P, 1 PT, 1 C, 2 CT)	<i>POF2.2.1.10</i> <i>POF 2: Preparation and inspection of drug/device</i> <i>Sub task 2.1: Check Drug integrity (color/appearance)</i> <i>Potential Use error 10: User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles)</i>

Table 36

Concluding results - Almost did not inject appropriate injection site

	Concluding Results
Description	Almost did not inject appropriate injection site (SR)
Number of participants who committed the close call	2 (1 PT, 1 C)
Total number of close calls committed	2 (1 PT, 1 C)
Possible root causes	Reliance on IFU (due to unintuitive step)
Risk(s) associated with Use error	POF 3: Inserting the needle into injections site Sub task 3.2: Choose appropriate injection site Potential Use error 32: User selects inappropriate or wrong injection site The resulting risks of the remaining use errors are moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 37

Concluding results - Almost injected with contaminated needle

	Concluding Results
Description	Almost injected with contaminated needle
Number of participants who committed the close call	1 (1 C)
Total number of close call committed	1 (1 C)
Possible root causes	Location of cautions on IFU's cover
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.6: Remove cap Potential Use error 30: User does not use device immediately when cap/RNS is removed The resulting risks of the remaining use errors are moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 38

Concluding results - Almost did not store PFS in refrigerator

	Concluding Results
Description	Almost did not store PFS in refrigerator
Number of participants who committed the close call	1 (1 C)
Total number of close calls committed	1 (1 C)
Possible root causes	Negative transfer Reliance on IFU due to unintuitive step
Risk(s) associated with Use error	POF 1: Safe transport and storage by user Sub task 1.1: Box handling Potential Use error 01: User does transport or store device in improper way The resulting risks of the remaining use errors are low for the possible failure causes. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 39

Concluding Results - Inspecting fluid contained within the PFS and calls service number for support

	Concluding Results
Description	Inspecting fluid contained within the PFS and calls service number for support
Number of participants who committed the close call	0
Total number of close calls committed	0
Possible root causes	none
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.1: Check Drug integrity (color/appearance) Potential Use error 10: User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles) The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 40 Operational difficulty summary

Use difficulty description	Number of participants who experienced the difficulty	Total number of use difficulties experienced
Struggled to identify expiration date on PFS	6 (1 P, 2 C, 2 CT, 1 HT)	10 (3 P, 2 C, 4 CT, 1 HT)
Believed PFS's fluid should be cloudy	1 (1 P)	3 (3 P)

Table 41 Concluding Results - Struggled to identify expiration date on PFS

	Concluding Results
Description	Struggled to identify expiration date on PFS
Number of participants who committed the use difficulty	6 (1 P, 2 C, 2 CT, 1 HT)
Total number of use difficulties committed	10 (3 P, 2 C, 4 CT, 1 HT)
Possible Failure Causes	Expiration Date Format
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.2: Check expiration date Potential Use error 12: User does not check expiration date The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 42 Concluding Results - Believed PFS's fluid should be cloudy

	Concluding Results
Description	Believed PFS's fluid should be cloudy
Number of participants who committed the use difficulty	1 (1 P)
Total number of use difficulties committed	3 (3 P)
Possible Failure cause	Formatting of IFU Step 2's text
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.1: Check Drug integrity (color/appearance) Potential Use error 10: User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles) The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

SUPPLEMENTAL HF VALIDATION PFS WITH QUICK TIPS

8.8.1 Number and type of test participants

A total of 19 individuals representing three distinct user groups (RA patients, prospective caregivers, and HCPs) participated in the summative usability test. Additionally, 10 participants received training before the test session. And, within the RA patient and caregiver user groups, some participants were injection-naïve (i.e., did not have experience using injection devices) and some participants were injection-experienced, of which one participant with Humira® pre-filled syringe experience, and one participant with Humira® auto-injector experience. The 19-participant test included representatives of the following user groups:

Table 43 Distribution of participants across user groups and sub-groups

User Group	Trained			Untrained			Overall
	Injection-experienced	Injection-naïve	Total	Injection-experienced	Injection-naïve	Total	
RA patients	2	1	3	2	1	3	6
Prospective caregivers	1	2	3	2	1	3	6
HCPs	4	N/A	4	3	N/A	3	7
Overall	7	3	10	7	2	9	19

8.8.2 Test participant training

Ten out of 19 participants received 15-30 minutes of one-on-one training from an independent Certified Diabetes Nurse Educator with injection training experience. This nurse, who was not affiliated with BI, was contracted by (b) (4) to deliver the training to the test participants.

During training, the trainer oriented each participant to the PFS and its associated IFU and QGS, provided a demonstration on how to handle the PFS, and then asked the participant to do a “teach back” simulated injection into the injection cushion provided. The trainer intervened when necessary during the teach back session to ensure that the participant performed all steps correctly, just as she would in a real training session. As such, the training closely matched the training that is expected actual end users to receive upon product launch.

Trained participants’ test sessions occurred at least two hours and up to three days after their training session. This training delay properly simulated the real-world use scenario, in which users would likely inject the first dose a few hours or days after receiving training and after picking up the PFS from the pharmacy. Participants did not have access to the PFS, the IFU, or QGS during the period following training and up until the test session. As such, participants were not able to prepare for the test beyond participating in their training session (i.e., there was no opportunity to study or refresh on the product details).

Table 45 Safety-related use error summary

Use error description	Number of participants who committed the use error	Total number of use errors committed	Risk(s) associated with the use error
Did not check expiration date	10	20	<i>POF2 – 2.2</i> : User does not check expiration date.
Did not inspect PFS for cracks or damage	5	10	<i>POF2 – 2.4</i> : User does not check for damages, cracks or leakage and risks using of damaged device.
Did not check fluid clarity	5	10	<i>POF2 – 2.1</i> : User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles).
User moved device position during injection	1	6	<i>POF3 – 3.3</i> : User moves device position (e.g., twisting, tilting device position) during injection
Did not inject into appropriate injection site	3	5	<i>POF3 – 3.2</i> : User selects inappropriate or wrong injection site.
Recapped needle	2	3	<i>POF5 – 5.1</i> : User recaps the needle.
Did not clean injection site	3	3	<i>POF3 – 3.1</i> : User does not clean injection site.
Did not discard used PFS in sharps container	1	1	<i>POF5 – 5.1</i> : User discards device in an improper way.
Did not discard cap	1	1	<i>POF2 – 2.6</i> . Accessories are not kept away from children & pets
Did not use PFS immediately after uncapping	1	1	<i>POF2 – 2.6</i> : User does not use device immediately when cap/RNS is removed

Table 46 Safety related use errors

Use error description	Number of participants who committed the use error	Total number of use errors committed	Risk(s) identifier
Did not check expiration date	3	6	<i>POF2 – 2.2</i> : User does not check expiration date.
Did not inspect PFS for cracks or damage	2	3	<i>POF2 – 2.4.13</i> : User does not check for damages, cracks or leakage and risks using of damaged device.
Did not check fluid clarity	2	3	<i>POF2 – 2.1</i> : User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles).
User moved device position during injection	1	1	<i>POF3 – 3.35</i> : User moves device position (e.g., twisting, tilting device position) during injection
Did not inject into appropriate injection site	1	2	<i>POF3 – 3.2</i> : User selects inappropriate or wrong injection site.
Recapped needle	0	0	<i>POF5 – 5.1.46</i> : User recaps the needle.
Did not clean injection site	1	1	<i>POF3 – 3.1.17</i> : User does not clean injection site.
Did not discard used PFS in sharps container	0	0	<i>POF5 – 5.1.44</i> : User discards device in an improper way,
Did not discard cap	1	1	<i>POF2 – 2.6</i> . Accessories are not kept away from children & pets
Did not use PFS immediately after uncapping	0	0	<i>POF2 – 2.6</i> : User does not use device immediately when cap/RNS is removed

Table 48

Concluding Results - User does not check expiration date

	Concluding Results
Description	User does not check expiration date
Number of participants who committed the use error	Total: 3 (PTE2 x2) (CE1 x 2) (P1 x2) No Humira experienced users committed this use error
Possible root causes	Perceived responsibility, QGS information presentation, Perceived device suitability IFU Step 2's length
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.2: Check expiration date Potential Use error 12: User does not check expiration date The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 49

Concluding Results - User does not check for damages, cracks or leakage

	Concluding Results
Description	User does not check for damages, cracks or leakage
Number of participants who committed the use error	Total: 1 (P1 x 2) No Humira experienced users committed this use error
Possible root causes	QGS information presentation, Reliance on IFU and QGS
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.4: Check expiration date Potential Use error 12: User does not check for damages, cracks or leakage and risks using of damaged device The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 50 Concluding Results - User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles)

	Concluding Results
Description	User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles)
Number of participants who committed the use error	Total: 1 (P1 x 2) No Humira experienced users committed this use error
Possible root causes	QGS information presentation
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.1: Check Drug integrity (color/appearance) Potential Use error 10: User does not check for drug appearance (cloudy, discolored, frozen, contains flakes or particles) The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 51 Concluding Results - User moves device position (e.g., twisting, tilting device position) during injection

	Concluding Results
Description	User moves device position (e.g., twisting, tilting device position) during injection
Number of participants who committed the use error	Total: 1 (C1 x 6) No Humira experienced users committed this use error
Possible root causes	Ambiguous illustration,
Risk(s) associated with Use error	POF 3: Inserting the needle into injection site Sub task 3.3: Place device at correct angle Potential Use error 35: User moves device position (e.g., twisting, tilting device position) during injection The resulting risks of the remaining use errors are low to moderate depending on the possible failure cause. The single risks have been reduced as far as possible. Taking into account the medical benefits, each single remaining residual risk has been assessed as acceptable.

Table 52 Concluding Results - User selects inappropriate or wrong injection site

	Concluding Results
Description	User selects inappropriate or wrong injection site
Number of participants who committed the use error	None No Humira experienced users committed this use error
Possible root causes	N/A
Risk(s) associated with Use error	POF 3: Inserting the needle into injections site Sub task 3.2: Choose appropriate injection site Potential Use error 32: User selects inappropriate or wrong injection site Any remaining residual risk has been assessed as acceptable. In addition, the injection of BI 695501 is bi-weekly and injection sites will have healed if this use error were repeated.

Table 53 Concluding Results - User recaps needle

	Concluding Results
Description	User recaps needle
Number of participants who committed the use error	0 No Humira experienced users committed this use error
Possible root causes	N/A
Risk(s) associated with Use error	POF 5: Disposal of device Sub task 5.1: Dispose of the device and safety cap in appropriate container Potential Use error 46: User recaps needle Any remaining residual risk has been assessed as acceptable.

Table 54 Concluding Results - User does not clean injection site

	Concluding Results
Description	User does not clean injection site
Number of participants who committed the use error	1 (PT1 x 1) No Humira experienced users committed this use error
Possible root causes	QGS – information presentation
Risk(s) associated with Use error	POF 3: Inserting the needle into injection site Sub task 3.1: Clean injection site Potential Use error 17: User does not clean injection site The resulting risk of the use errors is low to moderate depending on the possible failure cause. Taking into account the medical benefits, remaining residual risk has been assessed as acceptable.

Table 55 Concluding Results - User does not discard device into sharps container

	Concluding Results
Description	User does not discard device into sharps container
Number of participants who committed the use error	0 No Humira experienced users committed this use error
Possible root causes	N/A
Risk(s) associated with Use error	POF 5: Disposal of device Sub task 5.1: Dispose of the device and safety cap in appropriate container Potential Use error 44: User discards device in an improper way Any remaining residual risk has been assessed as acceptable.

Table 56 Concluding Results - User does not discard cap

	Concluding Results
Description	User does not discard cap
Number of participants who committed the use error	1 (H3 x 1) No Humira experienced users committed this use error
Possible root causes	Needle cap design
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.6: Remove cap Potential Use error 08: Accessories are not kept away from children & pets The resulting risk of the use moderate. Taking into account the medical benefits, remaining residual risk has been assessed as acceptable.

Table 57 Concluding Results - User does not use device immediately when cap/RNS is removed

	Concluding Results
Description	User does not use device immediately when cap/RNS is removed
Number of participants who committed the use error	0 No Humira participants committed the use error.
Possible root causes	N/A
Risk(s) associated with Use error	POF 2: Preparation and inspection of drug/device Sub task 2.6: Remove cap Potential Use error 30: User does not use device immediately when cap/RNS is removed Any risk of the use error is moderate. Taking into account the medical benefits, remaining residual risk has been assessed as acceptable.

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER SOURCES

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,^a along with postmarket medication error data, we reviewed the following Cyltezo labels and labeling submitted by Boehringer Ingelheim on October 27, 2016.

- Container label
- Carton labeling
- Instructions for Use
- Prescribing Information (Image not shown)

G.2 Label and Labeling Images (not to scale)

Container Label



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

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/s/

CARLOS M MENA-GRILLASCA
08/14/2017

MISHALE P MISTRY on behalf of SARAH K VEE
08/14/2017

MISHALE P MISTRY
08/14/2017

QUYNHNHU T NGUYEN
08/15/2017

MEMORANDUM

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

DATE: July 19, 2017

TO: Badrul Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)
Office of New Drugs

FROM: Melkamu Getie-Kehtie, R.Ph., Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

Himanshu Gupta, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of surveillance analytical inspection at (b) (4)
[REDACTED]

Inspection summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical inspection of study 1297.8 (BLA 761058) at [REDACTED] (b) (4). The analyses conducted for 20051167 (PK assay), 20051168 and 20068727 (ADA assays), and 20051169 (NAb assay) performed under study 1297.8 were audited.

Form FDA 483 was issued at the inspection close-out. The final inspection classification is Voluntary Action Indicated (VAI).

Although objectionable findings were observed during this inspection, the findings did not impact the reliability of the

data from the audited study. Thus, we recommend accepting the data from study 1297.8 for further Agency review.

Inspected study

Study Number: 1297.8

Study Title: Pharmacokinetics and safety of BI 695501 in healthy subjects: a randomized, double-blind, single-dose, parallel-arm, active-comparator clinical Phase 1 study

Dates of clinical study conduct: 02/04/2014 (trial initiation)-06/20/2014 (trial completion)

Dates of sample analysis:

PK (20051167): 04/09/2014-07/10/2014

ADA (20051168): 06/12/2014-08/13/2014

ADA (20068727): 01/02/2015-02/24/2015

NAb (20051169): 06/12/2014-08/13/2014

Analytical site:

[REDACTED] (b) (4)

OSIS scientists Melkamu Getie-Keptie, R.Ph., Ph.D. and Himanshu Gupta, Ph.D. audited the analytical portion of the above cited analyses at [REDACTED] (b) (4) between [REDACTED] (b) (4)

The inspection included a thorough examination of the facility, equipment, records for method validation and study sample analysis, SOPs, sample management/storage documentation, and instrument audit trails, as well as interviews and discussions with management and staff.

At the conclusion of the inspection, a Form FDA 483 was issued for one objectionable issue. The Form FDA 483 observation (Attachment 1), the firm's response dated 06/15/2017 (Attachment 2) and additional response to OSIS reviewer's queries dated 07/06/2017 (Attachment 3), and our evaluation are presented below.

[REDACTED] (b) (4)

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Conclusion

An objectionable finding was observed during this inspection and a Form FDA 483 was issued. After reviewing the inspectional finding and the firm's responses to Form FDA 483, OSIS concludes that the objectionable finding did not impact the reliability of the data from the audited study.

We recommend accepting the data from study #1297.8 (BLA 761058) for further Agency (FDA) review.

Final Classification:

VAI:

(b) (4)

CC:

OTS/OSIS/Kassim/Choe/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au/Getie-Kehtie/Gupta

Draft: MG 7/11/2017, 7/16/2017, 7/18/2017; HG 07/14/2017, HG 07/17/2017

Edit: SA 07/14/2017, SA 7/17/2017, SA 7/18/2017, SA 7/19/2017;
SC 7/18/2017

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/ (b) (4)

OSI file #s: BE 7396

FACTS: (b) (4)

Attachment 1: Form FDA 483 observation

Attachment 2: First response to FDA 483 observation received from [REDACTED] (b) (4)

Attachment 3: Second response to FDA 483 observation received from [REDACTED] (b) (4)

Attachment 4: 20017926 protocol amendments (up to Amendment 15)

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/s/

STANLEY AU on behalf of MELKAMU GETIE KEBTIE
07/19/2017

HIMANSHU GUPTA
07/19/2017

STANLEY AU
07/19/2017
Acting TL

SEONGEUN CHO
07/19/2017

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

PATIENT LABELING REVIEW

Date: July 5, 2017

To: Badrul Chowdhury, MD, PhD
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

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

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Adewale Adeleye, Pharm.D., MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (nonproprietary name): CYLTEZO (adalimumab-xxxx¹)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761058

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

¹ A four letter suffix for the nonproprietary name for CYLTEZO has not been determined. FDA is using “-xxxx” as a placeholder for the suffix. “-xxxx” is not intended to be included in the final printed labels and labeling.

1 INTRODUCTION

On October 27, 2016, Boehringer Ingelheim Pharmaceuticals, Inc. submitted for the Agency's review a 351(k) Biologics License Application (BLA) for CYLTEZO (adalimumab-xxxx) injection, for subcutaneous use. Boehringer Ingelheim Pharmaceuticals, Inc. seeks approval for CYLTEZO (adalimumab-xxxx) as a biosimilar product to the single reference biologic product HUMIRA (adalimumab) injection, for subcutaneous use, licensed under BLA 125057 by AbbVie, Inc.

The Applicant has proposed CYLTEZO (adalimumab-xxxx) injection, for subcutaneous use to be licensed for the same indications as the single reference product HUMIRA (with the exception of those indications under orphan drug exclusivity), for the treatment of the following:

- **Rheumatoid Arthritis (RA):** Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA.
- **Juvenile Idiopathic Arthritis (JIA):** Reducing signs and symptoms of moderately to severely active polyarticular JIA in patients 4 years of age and older.
- **Psoriatic Arthritis (PsA):** Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA.
- **Ankylosing Spondylitis (AS):** Reducing signs and symptoms in adult patients with active AS.
- **Adult Crohn's Disease (CD):** Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. Reducing signs and symptoms and inducing clinical remission in these patients if they have also lost response to or are intolerant to infliximab.
- **Ulcerative Colitis (UC):** Inducing and sustaining clinical remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to immunosuppressants such as corticosteroids, azathioprine or 6-mercaptopurine (6-MP). The effectiveness of CYLTEZO has not been established in patients who have lost response to or were intolerant to TNF blockers.
- **Plaque Psoriasis (PsO):** The treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.

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 January 5, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for CYLTEZO (adalimumab-xxxx) injection, for subcutaneous use.

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

2 MATERIAL REVIEWED

- Draft CYLTEZO (adalimumab-xxxx) injection, for subcutaneous use MG and IFU received on October 27, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on June 13, 2017.
- Draft CYLTEZO (adalimumab-xxxx) injection, for subcutaneous use MG and IFU received on October 27, 2016, revised by the Review Division throughout the review cycle, and received by OPDP on June 12, 2017.
- Draft CYLTEZO (adalimumab-xxxx) injection, for subcutaneous use Prescribing Information (PI) received on October 27, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on June 13, 2017.
- Draft CYLTEZO (adalimumab-xxxx) injection, for subcutaneous use Prescribing Information (PI) received on October 27, 2016, revised by the Review Division throughout the review cycle, and received by OPDP on June 13, 2017.
- [ABP-TRADENAME] (adalimumab-xxxx) Review of Patient Labeling: Medication Guide and Instructions for Use dated August 23, 2016.
- Approved HUMIRA (adalimumab) injection, for subcutaneous use comparator labeling dated April 28, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG and IFU document using the Arial font, size 10 and 11 respectively.

In our collaborative review of the MG and IFU we have:

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- 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 presentation of information in the MG is consistent with the format of the approved MG for the reference product 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.

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
07/05/2017

ADEWALE A ADELEYE
07/06/2017

MARCIA B WILLIAMS
07/06/2017

LASHAWN M GRIFFITHS
07/06/2017

MEMORANDUM

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

DATE: July 03, 2017

TO: Badrul Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)
Office of New Drugs

FROM: Melkamu Getie-Kehtie, R.Ph., Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of routine clinical inspections conducted at
Auckland Clinical Studies Limited, Auckland, and
Christchurch Clinical Studies Trust, Christchurch, New
Zealand for BLA 761058

Inspection summary

The Office of Study Integrity and Surveillance (OSIS) arranged for clinical inspections of study 1297.8 (BLA 761058) that were conducted at Auckland Clinical Studies Limited, Auckland, New Zealand and Christchurch Clinical Studies Trust, Christchurch, New Zealand.

No significant deficiencies were observed at either of the sites and no Form FDA 483 was issued at the inspection closeout. The final inspection classifications for both sites are No Action Indicated (NAI).

After reviewing the inspectional findings, OSIS recommends accepting the clinical data from study 1297.8 for further FDA review.

Please note that EIR for an inspection conducted at SGS Belgium NV, Antwerpen, Belgium is pending. An addendum to the EIR review covering SGS Belgium NV will be provided at a later date.

Inspected study

Study Number: 1297.8

Study Title: Pharmacokinetics and safety of BI 695501 in healthy subjects: a randomized, double-blind, single-dose, parallel-arm, active-comparator clinical Phase 1 study

Dates of conduct: 02/04/2014-06/20/2014

Clinical sites: Auckland Clinical Studies Limited
3 Ferncroft Street
Auckland, New Zealand

Christchurch Clinical Studies Trust
31 Tuam Street
Christchurch, New Zealand

ORA investigator Sereen G Morgan-Murray audited the clinical portion of the above study at Auckland Clinical Studies Limited, Auckland, New Zealand between May 8 and May 12, 2017, and at Christchurch Clinical Studies Trust, Christchurch, New Zealand, between May 15 and May 18, 2017.

The inspections included a thorough examination of subject records, informed consent process, institutional review board approvals, test article accountability, randomization, adverse events, and case report forms. Reserve samples were collected from both sites.

At the conclusion of the inspections, investigator Sereen G Morgan-Murray did not observe any objectionable findings and did not issue Form FDA 483 to any of the inspected clinical sites.

Conclusion

After reviewing the inspectional findings, OSIS concludes that the clinical data for all sites from the audited study (1297.8) are reliable. Therefore, OSIS recommends accepting the clinical data from study 1297.8 for further review.

Final Classification:

NAI: Auckland Clinical Studies Limited, Auckland, New Zealand
FEI: 3006802751

Page 3 – Routine clinical inspections at Auckland Clinical Studies Limited, Auckland, and Christchurch Clinical Studies Trust, Christchurch, New Zealand

NAI: Christchurch Clinical Studies Trust, Christchurch, New Zealand

FEI: 3003412077

CC:

OTS/OSIS/Kassim/Choe/Kadavil/Turner-Rinehardt/Fenty-Stewart/Nkah

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas

OTS/OSIS/DGDBE/Cho/Haidar/Choi/Skelly/Au/Getie-Kebtie

Draft: MG 6/22/2017, 6/30/2017, 7/3/2017

Edit: SA 06/22/2017, 06/30/2017; SC 6/30/2017; 7/3/2017

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL SITES /Auckland Clinical Studies Limited, Auckland, New Zealand/BLA 761058_BI 695501 (proposed biosimilar to US-licensed Humira®

Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/CLINICAL SITES /Christchurch Clinical Studies Trust, Christchurch, New Zealand/BLA 761058_BI 695501 (proposed biosimilar to US-licensed Humira®

OSI file #s: BE 7396

FACTS: 11719204

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/s/

MELKAMU GETIE KEBTIE
07/03/2017

STANLEY AU
07/03/2017
Acting Team Lead

SEONGEUN CHO
07/03/2017

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

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

Memorandum

Date: June 26, 2017

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

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

Subject: BLA # 761058 – CYLTEZO™ (adalimumab-xxxx) injection,
for subcutaneous use (Cyltezo)

Reference is made to DPARP's consult request dated January 5, 2017, requesting review of the proposed Package Insert (PI), Carton/Container Labeling, Medication Guide (MG), and Instruction for Use (IFU) for Cyltezo.

OPDP has reviewed the proposed PI, Medication Guide, and Instructions for Use entitled, "BLA761058_BI_proposedcleanPI_PFS.docx" that was sent via e-mail from DPARP to OPDP on June 12, 2017. OPDP has no comments on the proposed PI at this time.

OPDP has also reviewed the proposed Carton/Container labeling entitled:

- "bl7420a.pdf"
- "ct7422a.pdf"
- "ct7594a.pdf"
- "l7421a.pdf"

that was sent via e-mail from DPARP to OPDP on June 23, 2017. OPDP has no comments on the proposed Carton/Container labeling at this time.

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 your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

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

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/s/

ADEWALE A ADELEYE
06/26/2017

MEMORANDUM

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

DATE: May 5, 2017

TO: Badrul Chowdhury, M.D., Ph.D.
Director,
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Office of New Drugs

FROM: Xikui Chen, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)
and
Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Deputy Director,
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Bioanalytical Inspection at (b) (4)
(b) (4)
(b) (4) sponsored by Boehringer
Ingelheim Pharmaceuticals, Inc.

Inspection Summary:

At the request of the Division of Pulmonary, Allergy, and Rheumatology Products in the Office of New Drugs (OND), the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of bioanalytical portions of Study 1297.8 at (b) (4)

Based upon the results of this inspection, we recommend that bioanalytical data in the study be accepted for Agency review.

Study Audited during this Inspection:

Study Number: 1297.8

Study Title: "Pharmacokinetics and Safety of BI695501 in Healthy Subjects: A Randomized, Double-Blind, Single-Dose, Parallel-Arm, Active-Comparator Clinical Phase 1 Study"

Analysis Dates: March 2016

OSIS scientists Xikui Chen, Ph.D. and Michael F. Skelly, Ph.D. conducted the inspection of bioanalytical portions of Study 1297.8 from (b) (4). (b) (4) assayed anti-adalimumab antibodies in samples taken at Day 1 (pre-dose) and Day 71 (post-dose) in Study 1297.8. (b) (4) employed a radioimmunoprecipitation assay selective for IgG reactive with the F(ab')₂ region of adalimumab, and with little reactivity for IgM, IgG3, or rheumatoid factor. The samples had been assayed previously for anti-adalimumab antibodies at another site, using assays with different specificity, selectivity, and sensitivity.

The bioanalytical portion of the audit included a thorough review of facilities and equipment, applicable bioanalytical SOPs, study records and correspondence, method validation records, and interviews and discussions with (b) (4) management and staff. Because this was (b) (4) only study submitted to FDA to this date, no additional studies were selected for a surveillance assessment of the site. Instead, the surveillance assessment was based on review of facilities, equipment, processes for electronic records, and interviews with (b) (4) staff.

There were no objectionable observations and at the conclusion of the inspection, no Form FDA-483 was issued at (b) (4)

Recommendation:

Based upon the inspectional findings, bioanalytical data from (b) (4) for Study 1297.8 are found reliable and acceptable for Agency review.

Xikui Chen, Ph.D.
DGDBE, OSIS

Michael F. Skelly, Ph.D.
DGDBE, OSIS

Final Classification:

NAI: [REDACTED] (b) (4)

CC:

OTS/OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller/Kadavil

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala

OTS/OSIS/DGDBE/Cho/Haidar/Skelly/Choi/Au

Draft: MFS 5/5/2017, XC 5/5/2017

Edits: SHH 5/5/2017

OSIS file #: BE7396

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/

Bioanalytical [REDACTED]

(b) (4)

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/s/

MICHAEL F SKELLY
05/05/2017

XIKUI CHEN
05/05/2017

SAM H HAIDAR
05/06/2017

CLINICAL INSPECTION SUMMARY

Date	April 11, 2017
From	Anthony Orenca M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader, for Kassa Ayalew, M.D., M.P.H. GCPAB Branch Chief Division of Clinical Compliance Evaluation/OSI
To	Stefanie Freeman, M.D., DPARP, Medical Officer Nikolay Nikolov, M.D., DPARP, Cross-Discipline Team Leader Sadaf Nabavian, Regulatory Project Manager Division of Pulmonary, Allergy and Rheumatology Products
NDA	BLA 761058
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Drug	BI 695501 proposed biosimilar to adalimumab
NME	No
Therapeutic Classification	BSUFA (Biosimilar) [351(k) application]
Proposed Indication	Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, plaque psoriasis
Consultation Request Date	December 16, 2016 (signed)
Summary Goal Date	April 28, 2017 (original)
Action Goal Date	July 27, 2017
BSUFA Date	August 27, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two foreign clinical sites (Drs. Stoilov and Klimiuk) and Boehringer Ingelheim (sponsor) were selected by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) for inspection of Study 1297.2 submitted in support of BLA 761058, a proposed biosimilar for adalimumab. The final CDER regulatory classification for Drs. Stoilov and Klimiuk is No Action Indicated (NAI). The preliminary regulatory classification of the sponsor inspection is Voluntary Action Indicated (VAI).

The study data derived from these clinical sites are considered reliable in support of the requested indication.

2. BACKGROUND

TNF-alpha plays a crucial role in both the pathologic inflammation and joint destruction characteristic of rheumatologic diseases such as rheumatoid arthritis. The anti-TNF drug Humira® (adalimumab) has received regulatory approval for the treatment of moderate to severe rheumatoid arthritis in the US, EU, and other countries. The rationale for conducting Study 1297.2 [VOLTAIRE-RA] was to establish safety and efficacy non-inferiority between BI 695501 and US-licensed Humira®. A single randomized clinical trial was submitted in support of the applicant's BLA, for the treatment of adult patients with rheumatoid arthritis.

The review division (DPARP) requested inspection of two clinical sites and the sponsor for this application. These sites primarily enrolled large numbers of study subjects and had differential efficacy findings across clinical study sites.

Study 1297.2

Study 1297.2 was a randomized, 58-week, double-blind, parallel-arm, multiple-dose, active-comparator trial of BI 695501 and US-licensed Humira® with a 48-week treatment period, in patients with active rheumatoid arthritis receiving background methotrexate treatment. Study patients with moderately to severely active rheumatoid arthritis, who were receiving methotrexate therapy, were randomized into the trial. Patients were assigned to receive either BI 695501 or US-licensed Humira® according to the randomization ratio and the stratification criteria. Each patient was to receive 40 mg of trial drug every 2 weeks by subcutaneous injection. The co-primary efficacy endpoints in this trial were the proportion of patients meeting the ACR 20 response criteria at Week 12 and the proportion of patients meeting the ACR 20 response criteria at Week 24.

Study 1297.2 was conducted in 138 clinical sites in 15 countries. Of the 645 patients who were initially randomized, 324 patients were in the BI 695501 group and 321 patients were in the US-licensed Humira® group. At Week 24, a total of 593 patients were re-randomized; 298 patients in the BI 695501 to BI 695501 group, 148 patients in the US-licensed Humira® to US-licensed Humira® group, and 147 patients in the US-licensed Humira® to BI 695501 group). The first subject was screened on February 4, 2015. The clinical cut-off date for the Week 32 analysis was on April 29, 2016.

The sponsor claimed that the co-primary efficacy endpoints of ACR20 response criteria at 12 and 24 weeks were met and demonstrated therapeutic equivalence of BI 695501 and US-licensed Humira treatment groups.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects Randomized	Inspection Date	Classification
Rumen Stoilov, M.D. University Multiprofile Hospital for Active Treatment “Sv. Ivan Rilski”, EAD 13, Urvich Street Sofia, Bulgaria 1612	Protocol 1297.2 Site 9940615 Subjects=18	February 6 to 9, 2017	NAI
Piotr Klimiuk, M.D. Gabinet Internistyczno-Reumatologiczny Ul. Legionowa 3 Bialystok, Poland 15-099	Protocol 1297.2 Site 9943907 Subjects=23	February 13 to 16, 2017	NAI
Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Rd/P.O. Box 368 Ridgefield, CT 06877-0368	Protocol 1297.2	February 21 to 28, 2017	Pending: Preliminary VAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data are unreliable.

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

Clinical Investigator

1. Rumen Stoilov, M.D., Bulgaria

The inspection was conducted from February 6 to 9, 2017. A total of 20 subjects were screened, 18 subjects were enrolled and randomized. All 18 subjects completed the study. An audit of the 18 randomized subjects' records enrolled at this site was conducted.

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

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

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

Data submitted by this clinical site appears to be acceptable in support of this specific indication.

2. Piotr Klimiuk, M.D., Poland

The inspection was conducted from February 13 to 16, 2017. A total of 30 subjects were screened, 23 enrolled and randomized, and 23 study subjects completed the study. An audit of the 23 randomized subjects' records enrolled at this site was conducted.

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

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

The data submitted by this clinical site appears to be acceptable in support of this specific indication.

Sponsor

3. Boehringer Ingelheim Pharmaceuticals, Inc

This inspection was conducted from February 21 to 28, 2017.

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

Responsibility for study monitoring was contracted out to (b) (4). Monitoring visits including study site closeout were reviewed; monitoring reports indicated that the sites received adequate periodic monitoring. IRB approvals, site study protocol deviations, serious adverse events and related monitoring reports were assessed, and oversight by the contract research organization appeared to be adequate. The sponsor and (b) (4) had regular periodic meetings to facilitate communication about study conduct issues.

A Form FDA 483 was issued at the end of the inspection for the sponsor's failure to adequately monitor the study. Specifically, the Clinical Operations Plan and the Medical Monitoring Plan were not approved until after sites were initiated, subjects were randomized and receiving investigational product, and routine monitoring visits were performed.

DCCE reviewer's comment: Despite delayed approval of the final version of the Clinical Operations Plan and Medical Monitoring Plan for Study 1297.2, there were no subject safety concerns or problems with data management identified prior to finalization of these documents.

The sponsor's written correspondence dated March 17, 2017, appeared adequate.

Despite the above regulatory deficiency which was not critical in nature, records reviewed indicated that the sponsor maintained adequate oversight of the clinical trial.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch, for
Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
04/11/2017

JANICE K POHLMAN
04/12/2017



U.S. FOOD & DRUG
ADMINISTRATION

Inspection Assignment Memorandum

User Fee: Yes, BSUFA

Surveillance: Yes

Directed: No

Application: Yes

Submission: Premarket Original

Entity: Contract Research Organization (CRO)

Date: 3/9/2017

From: Melkamu Getie-Kehtie, R.Ph., Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

To: ORAHQDFFIIOBBIMO@fda.hhs.gov

Preannounce: No

Priority: Yes

ORA Due Date: 6/19/2017

Compliance Program: 7348.001 (BE)

Program Assignment Code: 48001S (BIOSIMILAR)

Operation Code: 11 (Foreign)
31 (Sample Collection)
41 (Sample Analysis)

Application Number: BLA 761058

Product Name: BI 695501

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc, 900 Ridebury Road, Ridgefield, CT 06877
(203) 798-9988

Study/Protocol Number: 1297.8

Center Participation: ☐ Yes or ☒ No.

Joint Regulatory Agency Participation: ☐ Yes or ☒ No.

Establishment(s) for inspection	FEI Number	FACTS Number
Magdalena Petkova, SGS Belgium NV, Lange Beeldekensstraat 267, Antwerpen, Belgium	3011416087	11719204
Last clinical inspection: June 1-5, 2015	Form FDA 483 with three observations was issued. The Form FDA 483 and EIR are uploaded with the background material in ECMS	
Roderick Boyd Ellis-Pegler Auckland Clinical Studies Limited 3 Ferncroft Street, Auckland, New Zealand	Refer to ORA	11719204
No previous inspection history		
Christopher John Wynne Christchurch Clinical Studies Trust 31 Tuam Street, Christchurch, New Zealand	3003412077	11719204
No previous inspection history		

Note	Please contact the OSIS scientific point of contact (POC) at CDER-OSIS-SCIPOC-BE@fda.hhs.gov prior to the beginning of the inspection to verify the focus and intent of the inspection. We frequently receive real-time information from the review team that may change the focus of the inspection. Please follow the compliance program with emphasis on the specific instructions in the memorandum. If significant deviations are found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data, we request that you expand the scope of your inspection as necessary and email CDER-OSIS-SCIPOC-BE@fda.hhs.gov and cc CDER-OSIS-BEQ@fda.hhs.gov immediately. Send the following information to the respective email in the table.	
	CDER-OSIS-SCIPOC-BE@fda.hhs.gov	CDER-OSIS-BEQ@fda.hhs.gov
	Scientific questions/comments	Not applicable
	Significant deviations found during the inspection that may have impact on the safety of study subjects or accuracy and reliability of the data	

	Not applicable	EIR (when available in OSAR)
		Form FDA 483 and 483 responses
	Inspection findings at end of inspection	
	Not applicable	Post Inspection correspondence from establishment

If the endorsed EIR and exhibits are paper, send the documents to Angel Johnson, OSIS Project Specialist.
 Ms. Angel Johnson
 Project Specialist
 FDA/CDER/OTS/OSIS
 WO51 RM5331
 10903 New Hampshire Ave.
 Silver Spring, MD 20993-0002
 Fax Number: (301) 847-8748

Important: All post-inspection correspondence must be reviewed prior to issuing any post-inspection notification of compliance status.

BACKGROUND INFORMATION

This inspection memo provides pertinent information to conduct the inspection of the **clinical portion** of the following bioequivalence (BE) study(ies). Background materials are available in ECMS under the ORA folder.

IMPORTANT REMINDERS:

1. Inspections should be scheduled for no more than one week unless otherwise noted.
2. A 100% audit of the studies is not required unless noted (refer to the DATA AUDIT CHECKLIST section of this memo). If specific audit instructions are not provided, please audit as much as possible during the one week inspection.
3. If the assignment contains more than 3 studies, instructions to audit specific sections of the study will be included in the DATA AUDIT CHECKLIST section of this memo.
4. Please note that additional studies for the site may be added to the assignment no later than 2 weeks prior to the inspection start date. The additional studies may be added because more significant, complex or recent studies are received by OSIS, or specific study issues are identified after the initial assignment is issued. Addition of these additional studies **SHOULD NOT** extend the inspection duration at the site.

Do not reveal the studies to be inspected, drug names, or the study investigators to the site prior to the start of the inspections. You should provide this information during the inspection

opening meeting. Please note that the inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of completed sections A B, and C of this memo to the OSIS scientific POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov.

Refer to the DATA AUDIT CHECKLIST in Section C-Clinical Data Audit for additional information.

BLA 761058

Study #: 1297.8
Study Title: "Pharmacokinetics and safety of BI 695501 in healthy subjects: a randomized, double-blind, single-dose, parallel-arm, active-comparator clinical Phase 1 study"

Site 1: SGS Belgium NV (site 1001)
Investigator: Magdalena Petkova, M.D.
of Subjects: 160 (number of subjects screened)

Site 2: Auckland Clinical Studies Limited (site 2001)
Investigator: Roderick Boyd Ellis-Pegler, M.D.
of Subjects: 148 (number of subjects screened)

Site 3: Christchurch Clinical Studies Trust (site 2002)
Investigator: Christopher John Wynne, M.D.
of Subjects: 152 (number of subjects screened)

Please collect a list of bioequivalence studies performed at the site in the last 5 years. The list should include information on test and reference reserve samples retained at the site or at a third party for the bioequivalence studies. Refer to Table 1 for an example. Please do spot checks to verify that the lot number(s) listed in the table match the reserve samples in the clinical site storage.

Table 1

SL NO.	Study number	Drug Name	Fast/Fed	Sponsor	Submission	Study Conduct Dates	Reserve Samples	Quantity	Lot# for Test and Reference
1	XXXXX	Aspirin + Dipyridamole Capsules	Fast	XXXX	USFDA	Dec 24-Dec 31, 2014	At Site	300 for test, 200 for reference	XXXX and XXX
2	XXXXX	Montelukast	Fed	XXXXX	unknown	XXXXX	Third Party	two kits	XXXX and XXX
3	XXXXX	XXXXXXXX	Fast	XXXXXX	Pilot	XXXXX	Not retained	two bottle for test, two bottles for reference	XXXX and XXX

SECTION A – BLINDING CODES

RANDOMIZATION OR BLINDING: Because this is a randomized and blinded bioequivalence study, it is necessary to break the blind and use the treatment codes to verify and confirm that the

subjects were dosed according to the treatment randomization schedule. Please verify the following during the inspection:

For 1297.8, an Interactive Voice/Web Response System (IVRS/IWRS) was used to assign kit numbers.

- ☐ If the unblinding is handled through an IVRS/IWRS, please evaluate the following issues for the IVRS/IWRS:
 - a) Based on the information linking the subject number, randomization number, kit type (e.g., treatment group), and kit number, determine whether there were any issues or discrepancies.
 - b) Through use of an audit trail or other documentation, determine whether the site had access to the randomization schedule or the unblinding codes for subjects.
- ☐ If paper based blinding codes are available (e.g. scratch-of labels or sealed envelopes), unseal the blinding code for all subjects enrolled at the site AND for reserve samples and note the date and your initials on the envelope, if applicable. Collect a copy of the study randomization schedule, if available, unsealed blinding code for all subjects and the dosing logs from the firm/clinical investigator. In addition, include a photocopy of the unsealed blinding code with the reserve samples sent to DPA. If the blinding code was already unsealed, determine the reasons why. If a sealed blinding code is not available, please notify the OSIS scientific POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov, immediately.
- ☐ Review the treatment codes (e.g., test or reference article) on the Case Report Forms and verify that 100% of the subjects were dosed according to the study randomization schedule and the information is consistent with the study report information.
- ☐ If paper based blinding codes are available, collect a written statement or affidavit to confirm that the blinding code remained in the possession of the clinical site prior to dosing the first subject and until the FDA inspection, and for both the IVRS/IWRS and paper based blinding codes, collect a written statement or affidavit to confirm that the subjects remained blinded throughout the study. In the event the study related documentation is stored at an alternate site, verify by affidavit that the alternate site is independent of the applicant, packager and manufacturer.

SECTION B – RESERVE SAMPLES

The test product (BI 695501) in study 1297.8 is a biosimilar and there is no current regulatory requirement to retain reserves for biosimilars. However, if reserve samples were retained, from each shipment, please collect at least 10 dosage units for each of the following products (3 dosage units of 40 mg per 0.8 mL adalimumab for each of the three products below from each shipment may be collected if 10 dosage units are not available):

1. BI 695501–proposed biosimilar for adalimumab
2. US-licensed adalimumab (Humira[®])-reference product
3. EU-approved adalimumab (Humira[®])-reference product

In addition, verify that the lot numbers on the reserve sample containers match those in the study report for the studies mentioned above. Please also determine whether the site conducting the study (i.e., each investigator site) randomly selected and retained reserve samples from the shipments of drug product provided by the Applicant for subject dosing. For the reserve samples you will be collecting, take a photograph of the unblinded reserve sample containers (test, reference, and placebo, if applicable) showing the drug name, strength (or concentration), lot number, and expiration date, and exhibit in the EIR.

If the reserve samples are not adequate in quantity, notify the OSIS POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov immediately.

If no reserves were retained, please document in the EIR that no reserves were retained. Please also include information in the EIR indicating whether: a) the information in the study records regarding dosing of drug products (e.g. drug products administered, timing of dose administration, lots numbers of the administered test and reference drug products, any deviations relevant to dosing) is consistent with the information in the study report and b) the drug accountability records were able to be reconciled based on the available info at the site.

During the clinical site inspection, if reserve samples were retained, please:

- ☐ If the reserve samples were stored at a third party site, (1) collect an affidavit to confirm that the third party is independent from the applicant, manufacturer, and packager; and (2) request the reserve samples to be shipped back to the site so that the samples can be collected during the inspection. Additionally, verify that the site notified the applicant, in writing, of the storage location of the reserve samples.
- ☐ Obtain written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific bioequivalence studies, and that samples were stored under conditions specified in accompanying records. Document the signed and dated assurance on the facility's letterhead, or Form FDA 463a Affidavit.
- ☐ Collect and ship samples of the test and reference drug products **in their original containers** to the following address:

Lucinda (Cindy) Buhse, Ph.D.
Acting Director
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110
TEL: 1-314-539-2135

SECTION C – CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings, including discussion items at closeout, as evidence of the findings.

Data Audit Checklist

- ☐ Confirm that informed consent was obtained prior to the study procedures for all subjects enrolled in all studies.
- ☐ For each treatment group (BI 695501, US-licensed adalimumab [Humira[®]] or EU-approved adalimumab), audit the study records for a minimum of 30 subjects enrolled in Study 1297.8.
- ☐ Compare the study report submitted to FDA with the original documents at the site.
- ☐ Check for under-reporting of adverse events (AEs).
- ☐ Check for evidence of inaccuracy in the electronic data capture system.
- ☐ Check reports for the subjects audited.
 - o Number of subject records reviewed during the inspection: _____
 - o Number of subjects screened at the site: _____
 - o Number of subjects enrolled at the site: _____
 - o Number of subjects completing the study: _____
- ☐ Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- ☐ Confirm that site personnel followed SOPs during study conduct.
- ☐ Examine correspondence files for any applicant or monitor-requested changes to study data or reports.
- ☐ Confirm that adequate corrective actions were implemented for observations cited during the last inspection (if applicable).
- ☐ Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- ☐ Other comments:

Additional instructions to the ORA Investigator

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS scientific POC prior to commencement of the inspection. Therefore, we request that the OSIS scientific POC be contacted at CDER-OSIS-SCIPOC-BE@fda.hhs.gov for any further instructions, inspection related questions or clarifications before the inspection and also regarding any data anomalies or questions noted during review of study records on site.

If you issue Form FDA 483, please forward a copy to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or please forward a copy to the OSIS Project Specialist contact at the address below, if paper. If it appears that the observations may warrant an OAI classification, send notification to the OSIS scientific POC at CDER-OSIS-SCIPOC-BE@fda.hhs.gov and cc CDER-OSIS-BEQ@fda.hhs.gov, as soon as possible.

Remind the inspected site of the 15 business-day timeframe for submission of a written response to the Form FDA 483. In addition, please forward a copy of the written response as soon as it is received to CDER-OSIS-BEQ@fda.hhs.gov, if electronic or if paper, forward a copy to the OSIS Project Specialist contact at the address below.

If the endorsed EIR and exhibits are in OSAR (or in another electronic format), send the email notification regarding the availability of the documents in OSAR to CDER-OSIS-BEQ@fda.hhs.gov.

If the endorsed EIR and exhibits are submitted in paper format, send the endorsed EIR and exhibits to the OSIS Project Specialist at the address below.

OSIS Project Specialist: Ms. Angel Johnson
Project Specialist
FDA/CDER/OTS/OSIS
WO51 RM5331
10903 New Hampshire Ave.
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OSIS/Kassim/Taylor/Kadavil/CDER-OSIS-BEQ@fda.hhs.gov
OSIS/DNDBE/Bonapace/Dasgupta/Biswas/Ayala
OSIS/DGDBE/Cho/Choi/Skelly/Au

Draft: MG 3/7/2017, 3/8/2017

Edit: SA 3/7/2017, SA 3/8/2017

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/SGS Belgium NV, Antwerpen, Belgium

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Auckland Clinical Studies Ltd, Auckland, New Zealand

ECMS: Cabinets/CDER OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical Sites/Christchurch Clinical Studies Trust, Christchurch, New Zealand

OSI file #: 7396

FACTS: 11719204

Melkamu Getie
Kebtie -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=0013219608,
cn=Melkamu Getie Kebtie -S
Date: 2017.03.09 08:20:13 -05'00'

Melkamu Getie-Kebtie, R.Ph., Ph.D.

Stanley Au -S

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DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Stanley Au -S,
0.9.2342.19200300.100.1.1=2000331264
Date: 2017.03.09 10:26:06 -05'00'

Stanley Au, Pharm.D., BCPS

(Acting Team
Lead)

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

/s/

MELKAMU GETIE KEBTIE
03/10/2017

STANLEY AU
03/10/2017