CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761071Orig1s000

OTHER REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

From:	Jacqueline A. Spaulding MD, Medical Officer Division of Pediatric and Maternal Health (DPMH) Office of Drug Evaluation IV (ODE IV) Office of New Drugs (OND)
Through:	Erica Radden, MD, Lead Medical Officer John J. Alexander, MD, MPH, Deputy Division Director DPMH, ODE IV, OND
To:	Division of Pulmonary and Rheumatology Products (DPARP)
Drug:	HYRIMOZ™/GP2017 (proposed biosimilar to Humira [adalimumab]) [1]
Application Number:	BLA 761071 (IND 115732)
RE:	Review Section 8 of the proposed labeling
Applicant:	Sandoz Inc.
Proposed Indications:	Rheumatoid Arthritis (RA) in adults Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older Psoriatic Arthritis (PsA) in adults Ankylosing Spondylitis (AS) in adults Crohn's Disease (CD) in adults Ulcerative Colitis (UC) in adults Plaque Psoriasis (PsO) in adults

[1] HYRIMOZ is the proposed proprietary name and is only conditionally accepted for this product until the application is approved; GP2017 is the product code name.

Proposed dosage form & route of administration:
- Injection: 40 mg/0.8 mL in a single-dose pre-filled glass syringe (with BD UltraSafe Passive™ Needle Guard)
- Injection: 40 mg/0.8 mL in a single-dose pre-filled pen (Sensoready® Pen)

Proposed Pediatric Dosing Regimen:
Juvenile Idiopathic Arthritis (JIA):
- ≥ 30 kg (66 lbs.): 40 mg every other week

Consult Request:
DPARP requests assistance in review of Section 8 of Applicant's proposed labeling

Materials Reviewed
- GP2017 Agreed initial Pediatric Study Plan (iPSP) (IND 115732) [April 13, 2016]
- DPMH review of GP2017 (IND 115732) [November 17, 2016]
- M1 and M2 of BLA submission (BLA 761071) [October 30, 2017]
- DPMH consult request [December 20, 2017]

I. Consult and Regulatory Background

On August 25, 2016 Sandoz Inc. submitted BLA 761071 for GP2017, a proposed biosimilar to US-licensed Humira (adalimumab).[2] However, the BLA was withdrawn on October 21, 2016 because the manufacturing sites were not ready for Pre-License Inspection. The applicant resubmitted this BLA on October 30, 2017. Humira is a tumor necrosis factor (TNF) blocker licensed by AbbVie, Inc. and was first approved in 2002. Adalimumab is a monoclonal antibody that binds specifically to TNF alpha ligands and blocks interaction with cell surface TNF receptors. TNF is a cytokine involved in inflammatory and immune responses, and elevated TNF levels also play a role in the pathology of inflammatory diseases.[3]

Sandoz is seeking approval for the following indications**:**
1. Rheumatoid Arthritis (RA) in adults
2. Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older
3. Psoriatic Arthritis (PsA) in adults
4. Ankylosing Spondylitis (AS) in adults
5. Crohn's Disease (CD) in adults
6. Ulcerative Colitis (UC) in adults
7. Plaque Psoriasis (PsO) in adults

US-licensed Humira was also licensed in adults for Hidradenitis Suppurativa (HS) on November 23, 2015, and for uveitis on June 30, 2016. The uveitis indication was expanded down to patients 2 years of age and older on September 28, 2018. However, Sandoz is not requesting licensure for these indications.

[2] DPMH Consult Request (December 20, 2017)
[3] Current US-licensed Humira (adalimumab) labeling [September 28, 2018] in Drugs@FDA

Reference ID: 4341571

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Section 505B(l) of the FD&C Act provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a new "active ingredient" for purposes of PREA. Therefore, a pediatric assessment is required for each of the proposed GP2017 indications for which Sandoz is seeking licensure unless waived or deferred. The Agency confirmed agreement with the agreed iPSP on April 13, 2016.[4]

DPARP has specifically consulted DPMH for assistance in reviewing Section 8 of the applicant's proposed labeling.

Pediatric Study Plan and Assessment:
In the agreed iPSP, which was included in the BLA without any changes, the applicant proposes to demonstrate biosimilarity to US-licensed Humira and provides their proposed strategy to address PREA requirements and the respective justifications which are summarized in Table 1.

[4] IND 115732 GP2017 - Agreed iPSP (April 13, 2016)

Reference ID: 4341571

Table 1 Overview on the strategy how to address PREA requirements and justification/remarks for GP2017

Approved indications of the reference product	Strategy to address PREA requirements	Justification/Remarks
Dermatology		
Plaque psoriasis (PsO)	Full waiver for plaque PsO in the pediatric population	Evidence suggesting that Humira would be ineffective or unsafe in all pediatric age groups with plaque PsO
Gastroenterology		
Crohn's disease(CD)/pediatric Crohn's disease (PCD)	Partial waiver for PCD **patients younger than 6 years**	Necessary studies are impossible or highly impracticable
	(b) (4)	• (b) (4) • GP2017 is being developed as a proposed biosimilar product to Humira • Until expiration of orphan exclusivity (September 2021) for PCD, indication will not be claimed
	(b) (4)	
Ulcerative colitis (UC)	Partial waiver for UC **patients younger than 5 years of age**	Necessary studies are impossible or highly impracticable
	Deferral of the requirement to submit a pediatric assessment for UC for **children 5 years of age and older**	• Adequate pediatric information in reference product labeling not yet available • (b) (4)

Source: IND 115732 GP2017 Agreed iPSP (April 13, 2016), Table 1, pp.7-8/42

Reference ID: 4341571

Approved indications of the reference product	Strategy to address PREA requirements	Justification/Remarks
Rheumatology		
Rheumatoid arthritis (RA)/juvenile idiopathic arthritis (JIA)	Partial waiver for JIA patients **younger than 2 years**	Condition is rare in this age group and necessary studies are impossible or highly impracticable
	(b) (4)	• (b) (4) • GP2017 is being developed as a proposed biosimilar product to Humira • Until expiration of orphan exclusivity (September 2021) for JIA subpopulation 2 to 4 years of age, sub-indication will not be claimed
	Deferral of the requirement to submit a pediatric assessment for JIA for **children weighing** (b) (4) (b) (4) **<30 kg (66 lbs)**	Development of a pediatric presentation (b) (4) (b) (4)
	(b) (4)	
Psoriatic arthritis (PsA)	Full waiver for PsA in the pediatric population	Necessary studies are impossible or highly impracticable due to difficulty in making specific diagnoses of juvenile PsA in the pediatric age range
Ankylosing spondylitis (AS)	Full waiver for AS in the pediatric population	Necessary studies are impossible or highly impracticable due to difficulty in making specific diagnoses of juvenile AS in the pediatric age range

Source: IND 115732 GP2017 Agreed iPSP (April 13, 2016), Table 1, pp.7-8/42

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On July 31, 2017, Sandoz submitted an amendment to its agreed iPSP[5], in which they proposed the following two changes to the iPSP:

(1) Delay the timeline for the submission of the (b) (4) from 2017 in the agreed upon iPSP to 2019.
(2) (b) (4)

The applicant states the pediatric timeline was delayed as the planned August 2017 approval date was based on an August 2016 submission of the initial BLA. However, while the sponsor did submit their initial BLA in August of 2016, it was later withdrawn in October 2016 and resubmitted on October 30, 2017. The applicant contends that this delay will affect the timelines for the deferral of the requirement to submit a pediatric assessment for pediatric CD and the deferral of the requirement to submit a pediatric assessment for JIA in patients 2 to 4 years of age.

At the Pediatric Review Committee (PeRC) meeting on October 11, 2017[6] , the applicant's proposed amendments to the iPSP were discussed. Among other things, the PeRC did not agree to the changes in the timeline for the development of (b) (4). The PeRC recommended that DPARP not agree to extending the timeline until July 2019 and inform the applicant that it is premature to agree to the extension and the applicant will need to provide additional information on the work that has been completed in development (b) (4) for dosing in smaller pediatric patients.

The PeRC recommendations included the following:

1. Pediatric timelines for (b) (4) to be changed to July 2018 instead of July 2019 because the applicant has already missed their original timeline of submission in 2017.
2. The PeRC concurred with the full waiver for the Plaque Psoriasis, Psoriatic Arthritis and Ankylosing Spondylitis indications. Of note, in the Amended iPSP – Written response[7] DPARP recommended to the applicant that the full waiver for PsO in the pediatric population should be based on the rationale that the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients.
3. The PeRC agreed with the existing proposed waivers and deferrals, which were unchanged.

Of note, the applicant never reached agreement with the Agency on the proposed amended iPSP, and instead submitted the original agreed iPSP from April 2016 in the BLA submission.

Reviewer Comment: Due to the delay in review of this application following its withdrawal in October 2016 and resubmission in October 2017, the proposed extended timeline for the submission of (b) (4) in July 2019 in the amended iPSP, would now be reasonable and can be reflected in the due dates issued for the PREA Postmarketing Requirements in the approval letter.

Additionally, the applicant requested a full waiver of the PREA requirement to provide a pediatric assessment for the PsO indication based on safety concerns related to an increased risk

[5] IND 115732 GP2017 Amended PSP (July 31, 2017)
[6] PeRC Meeting Minutes (October 11, 2017)
[7] IND 115732 Amended iPSP – Written Response (October 27, 2017)

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of malignancy and infection associated with use of TNFα inhibitors. FDA's current view is that this safety information does not necessarily apply across the class of TNFα inhibitors and thus does not support a full waiver of the pediatric assessment for PsO based on safety. DPMH agrees with DDDP that a full waiver of the requirement for a pediatric assessment for PsO is instead justified because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients. As a class, TNFα inhibitors are not first-line agents for treatment of moderate to severe PsO in pediatric patients. However, etanercept, another TNFα inhibitor, is approved for pediatric use in the US for moderate to severe PsO in patients 4 years of age and older. Furthermore, newer, more narrowly targeted systemic agents, which might provide a better safety profile, have been approved for psoriasis in adults and are being evaluated for use in pediatric patients. Additionally, DDDP requested a use review which confirmed that pediatric use of TNFα inhibitors for psoriasis was small ((b) (4)% share of total use of all TNFs), and for adalimumab, was consequently even less. The PeRC reviewed the pediatric assessment outlined in the agreed iPSP for GP2017 on September 12, 2018. They concurred with the proposed waivers and deferrals, except for the PsO indication, they agreed with this alternate rationale for a full waiver.

Furthermore, in the Summary of Clinical Efficacy, the applicant proposes to extrapolate the pediatric information from US-licensed Humira to their proposed biosimilar, GP2017 in the context of their biosimilar development program only for JIA in patients 4 years and older. The applicant states that the justification for extrapolation excludes the indications for JIA in patients 2 to 4 years of age, or for Pediatric CD for this original BLA. Therefore, a deferral of the requirement to submit a pediatric assessment in JIA for patients 2 to 4 years of age and for pediatric CD in patients 6 to 17 years of age, including the relevant age-appropriate presentations, is appropriate and should be reflected in the postmarketing requirements.

II. DPMH Recommendations for Pediatric Use Information in Labeling

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. When substantial evidence does not exist to support a pediatric indication, pediatric information related to the unapproved use should generally be restricted to the Pediatric Use subsection only, to avoid an inference of an approved pediatric indication as required by 21 CFR 201.57(c)(9)(iv). However, if a specific risk has been identified for pediatric patients, this risk information must be described in the Pediatric Use subsection, and if appropriate, be placed in the Contraindications section or Warnings and Precautions section. In such cases, the Pediatric Use subsection must refer to the risk information in the Contraindications or Warnings and Precautions section. 21 CFR 201.57(c)(9)(iv) also describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population (also see the February 2013 draft Guidance for Industry and Review Staff Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling; when finalized, this guidance will represent the Agency's current thinking).

This DPMH-Pediatric team labeling review will specifically focus on edits to Section 1

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(Indication and Usage), Section 2 (Dosage and Administration), and Section 8.4 (Pediatric Use). DPMH's additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text.

Applicant's Proposed Labeling
1 INDICATIONS AND USAGE

1.2 Juvenile Idiopathic Arthritis
HYRIMOZ™ is indicated for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older. HYRIMOZ can be used alone or in combination with methotrexate.

Reviewer Comments: DPMH agrees with the applicant's proposed language.

Applicant's Proposed Labeling
2 DOSAGE AND ADMINISTRATION

The recommended dose of HYRIMOZ™ for patients 4 years of age and older with polyarticular juvenile idiopathic arthritis (JIA) is based on weight as shown below. MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with HYRIMOZ.

Patients (4 years of age and older)	Dose
≥30 kg (66 lbs)	40 mg every other week (HYRIMOZ™ single-dose pre-filled Sensoready® Pen or HYRIMOZ™ single-dose pre-filled syringe)

Healthcare providers should be advised that there is no dosage form for HYRIMOZ which allows weight-based dosing (b) (4) for children below 30 kg. Adalimumab products have not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

Reviewer Comments: DPMH agrees with the applicant's proposed language.

Applicant's Proposed Labeling
8 USE IN SPECIFIC POPULATIONS

8.4 Pediatric Use

Safety and efficacy of HYRIMOZ™ in pediatric patients for uses other than polyarticular juvenile idiopathic arthritis (JIA) have not been established. Due to its inhibition of TNFα, adalimumab products administered during pregnancy could affect immune response in the in utero-exposed newborn and infant. Data from eight infants exposed to adalimumab in utero suggest adalimumab crosses the placenta [*see Use in Specific Populations (8.1)*]. The clinical significance of elevated adalimumab levels in infants is unknown. The safety of administering live or live-attenuated vaccines in exposed infants is unknown. Risks and benefits should be considered prior to vaccinating (live or live-attenuated) exposed infants.

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Post-marketing cases of lymphoma, including hepatosplenic T-cell lymphoma and other malignancies, some fatal, have been reported among children, adolescents, and young adults who received treatment with TNF-blockers including adalimumab products [*see Boxed Warning and Warnings and Precautions (5.2)*].

Juvenile Idiopathic Arthritis

In Study JIA-I, adalimumab was shown to reduce signs and symptoms of active polyarticular JIA in patients 4 to 17 years of age [*see Clinical Studies (14.2)*]. Adalimumab products have not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg.

The safety of adalimumab in patients in the polyarticular JIA trials was generally similar to that observed in adults with certain exceptions [*see Adverse Reactions (6.1)*].

Reviewer Comments: DPMH agrees with the applicant's proposed language. US-licensed Humira has unexpired orphan exclusivity for pediatric CD and JIA in patients 2 to 4 years of age. The applicant is not requesting licensure for those indications. Therefore, reference to these indications and subpopulations should be excluded from labeling.

DPMH Actions and Labeling Recommendations:

DPMH reviewed the applicant's proposed labeling and participated in the internal meetings from May 2018 to June 2018. Recommended labeling for the pediatric population based on labeling discussions between DPARP, and DPMH is provided per 21 CFR 201.57(c)(9)(iv). DPMH considered the alignment of GP2017 labeling with that of the currently approved US-licensed Humira labeling, where applicable, in our recommendations. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested in this review.

Reference ID: 4341571

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/s/

ERICA D RADDEN
10/29/2018

JOHN J ALEXANDER
10/29/2018

ADDENDUM MEMORANDUM

REVIEW OF LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 9, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761071
Product Name and Strength:	Hyrimoz (adalimumab-adaz) 40 mg/0.8 mL
Applicant/Sponsor Name:	Sandoz Inc.
FDA Received Date:	Combination Product (Biologic-Device)
OSE RCM #:	2016-2029-1 and 2017-2361-1
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the Hyrimoz and Hyrimoz Sensoready Pen Reference Guide (QRG) from a medication error perspective. Sandoz is seeking licensure for two Hyrimoz presentations: 40 mg/0.8 mL in a single-dose pre-filled glass syringe (with BD UltraSafe Passive™ Needle Guard); and 40 mg/0.8 mL in a single-dose pre-filled pen (Sensoready® Pen). The reference product, US-licensed Humira (adalimumab) (BLA 125057), was approved on December 31, 2002.

2 CONCLUSION

The QRG for Hyrimoz and Hyrimoz Sensoready Pen is acceptable for the adult populations from a medication error perspective. We have no further recommendations at this time.

Reference ID: 4331919

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 30, 2017

Quick Reference Guide for Autoinjector

Quick Reference Guide for Prefilled Syringe

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/s/

TERESA S MCMILLAN
10/09/2018

SARAH K VEE
10/09/2018

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

PATIENT LABELING REVIEW

Date:	September 28, 2018
To:	Sally Seymour, MD Acting Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Aman Sarai, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFUs)
Drug Name (nonproprietary name):	HYRIMOZ (adalimumab-adaz)[1]
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	761071
Applicant:	Sandoz Inc.

[1] A four letter suffix for the nonproprietary name for HYRIMOZ has been conditionally accepted until such time that the application is approved.

1 INTRODUCTION

On October 30, 2017, Sandoz, Inc. resubmitted for the Agency's review Biologics License Application (BLA) 761071 for GP2017 (adalimumab-adaz), a proposed biosimilar to Humira. BLA 761071 was orginially submitted on August 25, 2016 but was withdrawn as FDA's expectations regarding the Pre-License Inspection (PLI) scheduling could not be met for one of the proposed manufacturing sites.

Sandoz is seeking licensure of HYRIMOZ (adalimumab-adaz) injection, for subcutaneous use for the following indications:

- **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 HYRIMOZ 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.

Sandoz is seeking licensure for two Hyrimoz presentations: 40 mg/0.8 mL in a single-dose pre-filled glass syringe (with BD UltraSafe Passive™ Needle Guard); and 40 mg/0.8 mL in a single-dose pre-filled pen (Sensoready® Pen).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on November 28, 2017 and November 22, 2017, respectively for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for HYRIMOZ (adalimumab-adaz) injection, for subcutaneous use.

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

2 MATERIAL REVIEWED

- Draft HYRIMOZ (adalimumab-adaz) MG and IFUs received on October 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 13, 2018.
- Draft HYRIMOZ (adalimumab-adaz) Prescribing Information (PI) received on October 30, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 13, 2018.
- Approved HUMIRA (adalimumab-adbm) injection MG labeling dated August 2, 2018.

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 reformatted the MG and IFUs using the Arial font, size 10.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs 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 IFUs meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

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/s/

AMANPREET K SARAI
09/28/2018

MARCIA B WILLIAMS
09/28/2018

ADEWALE A ADELEYE
09/28/2018

LASHAWN M GRIFFITHS
09/28/2018

ICCR QUALITY SYSTEM REVIEW MEMO

Date:	September 25, 2018
To:	Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): Anh-Thy Ly -OPRO/OPQ, CDER,,Ahn-thy.ly@fda.hhs.gov
CC:	Office of Combination Product, Combination@fda.hhs.gov
Through:	Laurence Coyne, OHT 6, DHT 6C, RRT & FFDT, CDRH, WO 66, Rm1526, laurence.coyne@fda.hhs.gov
From:	Philip Lafleur, MPAS, OHT 6, DHT 6C, RRT & FFDT philip.lafleur@fda.hhs.gov
Applicant/Licensure:	Sandoz Inc. 100 College Road West Princeton, NJ FEI: 3004828473
Submission (Type & Number):	BLA-761071
Combination Product Name:	GP2017 (adalimumab) Solution for injection
Combination Product Indications for Use:	Rheumatoid Arthritis
Device Constituent (Type):	Auto injector or Pen Prefilled Syringe
ICCR Sharepoint Tracking Number:	BLA-761071
ICCR CTS Tracking Number:	BLA-761071
Pre-Approval Facility	No

Reference ID: 4326700

Inspection:

Documentation Review (Status): Response Adequate

CDRH/OC Recommendation: **Approvable**

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for BLA-761071.

PRODUCT DESCRIPTION

Adalimumab is an inhibitor of tumor necrosis factor, a protein that is overproduced in certain autoimmune conditions, including rheumatoid arthritis, which leads to tissue destruction in joints, mucosa or skin. Adalimumab works by targeting and blocking this protein that contributes to disease symptoms.

REGULATORY HISTORY

The following facility was identified as being involved in the manufacturing and/or development of the combination product, GP2017 (adalimumab) Solution for injection, in BLA-761071.

Combination Product Applicant

Sandoz Inc.

100 College Road West

Princeton, NJ

FEI: 3004828473

Responsibility – Manufacturing and primary packaging.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 2/22/2018 to 3/2/2018. The inspection covered drug CGMP and was classified VAI.

Reference ID: 4326700

Inspection Recommendation:

Inspections are not needed since all firms were inspected this year.

Finished Combination Product Manufacturers

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Responsibility – Manufacturing and primary packaging.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4). The inspection covered drug CGMP and was classified VAI.

Inspection Recommendation:

Inspections are not needed since all firms were inspected this year.

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Responsibility – Assembly and packaging of final product.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted (b) (4). The inspection covered biologic drug CGMP and was classified NAI.

Inspection Recommendation:

Inspections are not needed since all firms were inspected this year.

DOCUMENTATION REVIEW

Device Consituent Part Type: Prefilled Syringe

Device Consituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, Inhaler, Vaginal Ring, IUD

Combination Product BLA-761071 Proposed Indication for Use: Rheumatoid Arthritis

Review the documentation (NDA, ANDA, or BLA) to address the items below in order to make an evaluation of the risk of the combination product. Check the appropriate answer. For any items where the information was not provided in the application, check unknown and disregard.

1. Was the last inspection of the finished combination product manufacturing site, (b) (4), OAI for drug or device observations?	YES ☐	NO ☒	NA ☐
2. Is the device constituent a PMA or class III device?	YES ☐	NO ☒	UNK ☐
3. Is the final combination product meant for emergency use?	YES ☐	NO ☒	UNK ☐
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☐	NO ☒	UNK ☐
5. Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES ☐	NO ☒	UNK ☐
6. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES ☐	NO ☒	UNK ☐
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES ☐	NO ☒	UNK ☐

cGMP Risk: ☒ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.

☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not

warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant:	Sandoz Inc. 100 College Road West Princeton, NJ FEI: 3004828473
Finished Combination Product Manufacturer:	(b) (4) FEI: (b) (4) (b) (4) FEI: (b) (4)

Applicable Sites (b) (4)	Management Responsibility, 21 CFR 820.20 The firm provided a summary of how the firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).	YES ☒	NO ☐

Reference ID: 4326700

(b) (4) [Site3]☐	The firm provided a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.	YES ☒	NO ☐
	21 CFR 820.20 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) All documents provided by the firm were pertaining to drug manufacture only. The requirements of 21 CFR 820.20 were not addressed. *21 CFR 820.20 Deficiency* 1. (b) (4) has inadequately addressed the requirement for 21 CFR 820.20, management responsibility. Please provide a summary of how (b) (4) management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). 9/25/2018 Additional information request: The firm provided an SOP that adequated described compliance with this portion of the Quality System.		
Applicable Sites (b) (4)	Design Controls, General, 21 CFR 820.30 The firm explained how it utilized the design control process to develop the combination product under review and provided a description of its design control procedures.	YES ☒	NO ☐
	The firm provided a copy or a summary of the plan used to design the combination product.	YES ☒	NO ☐
[Site3]☐	*21 CFR 820.30 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)* Sandoz, the parent corporation, is responsible for the design of the product. 9/25/2018 Additional information request: The firm provided an SOP that adequated described compliance with this portion of the Quality System.		
Applicable Sites (b) (4)	Purchasing Controls, 21 CFR 820.50 The sponsor firm should summarize its procedure(s) for purchasing controls.	YES ☒	NO ☒
	The summary should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.	YES ☒	NO ☒

Reference ID: 4326700

[redacted] (b) (4) [Site3] ☐	The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process.	YES ☒	NO ☐
	The summary should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.	YES ☒	NO ☐
	The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.	YES ☒	NO ☐
	The firm should provide a description of how it applied the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).	YES ☒	NO ☐

21 CFR 820.50 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)

All documents provided by the firm were pertaining to drug manufacture only. The requirements of 21 CFR 820.50 were not addressed.

21 CFR 820.50 Deficiency

2. [redacted] (b) (4) has inadequately addressed the requirement for 21 CFR 820.50, purchasing controls. Please provide a summary of the procedure(s) for purchasing controls at [redacted] (b) (4). The summary should:

a. Describe [redacted] (b) (4) supplier evaluation process and describe how it will determine type and extent of control you will exercise over suppliers.

b. Define how [redacted] (b) (4) maintain records of acceptable suppliers and how [redacted] (b) (4) addresses the purchasing data approval process.

c. Explain how [redacted] (b) (4) will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

9/25/2018 Additional information request: The firm provided an SOP that adequated described compliance with this portion of the Quality System.

Reference ID: 4326700

Applicable Sites (b) (4) [Site3]☐	Corrective and Preventive Action (CAPA), 21 CFR 820.100 The sponsor firm should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.	YES ☒	NO ☐
	The CAPA system should require: a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;	YES ☒	NO ☐
	b. Investigation of nonconformities and their causes;	YES ☒	NO ☐
	c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and	YES ☒	NO ☐
	d. Verification or validation of the actions taken.	YES ☒	NO ☐

21 CFR 820.100 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)

All documents provided by the firm were pertaining to drug manufacture only. The requirements of 21 CFR 820.100 were not addressed.

21 CFR 820.100 Deficiency

3. (b) (4) and (b) (4) have inadequately addressed the requirement for 21 CFR 820.100, corrective and preventive actions. Please summarize the procedure(s) for (b) (4) and (b) (4) Corrective and Preventive Action (CAPA) System. The CAPA system should require:
   a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
   b. Investigation of nonconformities and their causes;
   c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
   d. Verification or validation of the actions taken.

9/25/2018 Additional information request: The firm provided an SOP that adequated described compliance with this portion of the Quality System.

Reference ID: 4326700

Applicable Sites (b) (4)	Installation, 21 CFR 820.170 (check none if Installation is not required for the combination product) If applicable for the combination product, the firm should provide a summary of how it has established installation, inspection instructions, and test procedures for the installation of the combination product.	YES ☒	NO ☐
	21 CFR 820.170 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)		
[Site3] ☐ None: ☐	All documents provided by the firm were pertaining to drug manufacture only. The requirements of 21 CFR 820.170 were not addressed. *21 CFR 820.170 Deficiency* 4. (b) (4) has inadequately addressed the requirement for 21 CFR 820.170, Installation. If applicable for the combination product, please provide a summary of how your firm has established installation, inspection instructions, and test procedures for the installation of the combination product. 9/25/2018 Additional information request: The firm provided an SOP that adequated described compliance with this portion of the Quality System.		

Applicable Sites (b) (4) [Site3]☐ None: ☐	Servicing, 21 CFR 820.200 (check none if Servicing is not required for the combination product) Where servicing is a specified requirement for the combination product, the firm should provide a summary of how it has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.	YES ☒	NO ☐
	21 CFR 820.200 In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product) All documents provided by the firm were pertaining to drug manufacture only. The requirements of 21 CFR 820.200 were not addressed. *21 CFR 820.200 Deficiency* 5. (b) (4) has inadequately addressed the requirement for 21 CFR 820.200, Servicing. Where servicing is a specified requirement for the combination product, please provide a summary of how your firm has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements. 9/25/2018 Additional information request: The firm provided an SOP that adequated described compliance with this portion of the Quality System.		
Applicable Sites (b) (4) [Site3]☐	Production and Process Controls The sponsor should provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☒	NO ☐

Reference ID: 4326700

None: ☐	*Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)* All documents provided by the firm were pertaining to drug manufacture only. The requirements of Production and Process Control were not addressed. *Production and Process Control Deficiency* 6. Please provide a summary of the procedure(s) for environmental and contamination controls of (b) (4) or the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product.		
Applicable Sites (b) (4)	The sponsor should provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☒	NO ☐
[Site3]☐ None: ☐	*Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)* All documents provided by the firm were pertaining to drug manufacture only. The requirements of Production and Process Control were not addressed. *Production and Process Control Deficiency* 7. Please provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process. 9/25/2018 Additional information request: The firm provided an SOP that adequated described compliance with this portion of the Quality System.		

Applicable Sites (b) (4) [Site3] ☐ None: ☐	The sponsor should explain how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. The firm should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. The firm should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☒	NO ☐

Production and Process Control In-Depth Review Including Review of relevant SOPs/Procedures/Test Reports and Documentation (For High Risk Combination Product)

All documents provided by the firm were pertaining to drug manufacture only. The requirements of Production and Process Control were not addressed.

Production and Process Control Deficiency

8. Please explain how (b) (4) will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. (b) (4) should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. (b) (4) should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product.

9/25/2018 Additional information request: The firm provided an SOP that adequated described compliance with this portion of the Quality System.

Deficiencies Identified. After reviewing the provided documents related to 21 CFR Part 4 requirements during the documentation review of the application in reference to applicable 21 CFR 820 regulations of the finished combination product, the following deficiencies have been identified. Please provide complete responses as well as where in the application we can find the information, if already provided.

Reference ID: 4326700

1. Your firm has inadequately addressed the requirements for 21 CFR 820.20, Management Responsibility. Please provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).

2. Your firm has inadequately addressed the requirements for 21 CFR 820.30, Design Controls. Please explain your firm utilized the design control process to develop the combination product under review. Please provide descriptions of the design control procedures for your firm. The procedures' descriptions must include how the requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are fulfilled. Please provide a copy or a summary of the plan used to design the combination product. Please explain how your firm utilized the design control process to develop the combination product under review.

3. Your firm has inadequately addressed the requirements for 21 CFR 820.50, Purchasing Controls. Please provide a summary of the procedure(s) for purchasing controls. The summary should:
    a. Describe your supplier evaluation process and describe how it will determine the type and extent of control to be exercised over suppliers;
    b. Define how the records of acceptable suppliers will be maintained;
    c. Address the purchasing data approval process; and
    d. Explain how your firm will balance purchasing assessment and receiving acceptance to ensure that products are acceptable for their intended use.

    Please explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Please provide a description of how your firm will apply purchasing controls to the suppliers/contractors used in the manufacturing of the combination product.

4. Your firm has inadequately addressed the requirements for 21 CFR 820.100, Corrective and Preventive Actions. Please summarize the procedure(s) for your firm's Corrective and Preventive Action (CAPA) System. The CAPA system should require:
    a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
    b. Investigation of nonconformities and their causes;
    c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
    d. Verification or validation of the actions taken.

9/25/2018 Additional information request: The firm provided SOP documents that adequated described compliance with the required portions of the Quality System.

Reference ID: 4326700

Please note that for combination products manufactured under the CGMP drug operating system, the Applicant/Licensure must also fulfill the requirements under 21 CFR Part 4.4b to show compliance to 21 CFR Part 4 for the finished combination product. To assist in the preparation of the above summaries related to the 21 CFR 820.20, 21 CFR 820.30, 21 CFR 820.50 and 21 CFR 820.100, we recommend the following FDA Guidance: 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003) located at the link: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm.

RECOMMENDATION

The approvability of application for BLA-761071 GP2017 (adalimumab) Solution for injection should be approved for the following reasons:

1. Review of documentation provided by the firm revealed adequate compliance with the portions of the quality system required for the manufacture of this product.
2. No inspections are needed since all firms had recent NAI/VAI inspections.

OC Decision: Approvable (Recommend approval to CDER)

Reviewer: Phillip H. Lafleur -S
2018.09.26 09:24:12 -04'00'

Philip Lafleur, MPAS

Branch Chief or Lead CSO: Laurence D. Coyne -S
2018.09.26 09:43:17 -04'00'

Reference ID: 4326700

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4326700

[END OF FORM or TEMPLATE – REMOVE CONTENT FROM THIS LINE TO END OF DOCUMENT PRIOR TO PUBLISHING]

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Change Control, Change History

Change Control

Version	Document Author	Document Approver	Date Approved
1.00	Name, Title, Office	Name, Title, Office	MM/DD/YYYY

Complete Change Control table (all versions) retained in SWIFT Docs.

Change History

Version	Description of Changes	Form ID	Date Effective
1.00	Initial Controlled Version.	01103.02.01	MM/DD/YYYY

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Action Codes: R – Review (with comments, follow-up review requested); C – Concur (with or without comments, no further review required).

Reference ID: 4326700

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHUONG N TON
09/27/2018
Administratively checked into DARRTS by Project Manager on behalf of the reviewer

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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

PLLR Labeling Memorandum

Date: August 31, 2018 **Date consulted:** December 20, 2017

From: Carrie Ceresa, Pharm D., MPH, Clinical Analyst, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader
Division of Pediatric and Maternal Health

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

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

Drug: Hyrimoz **(**adalimumab-(b) (4)); GP2017*[1]

BLA: 761071

Applicant: Sandoz

Subject: Pregnancy and Lactation Labeling Rule (PLLR) labeling format

Proposed Indications: Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA), Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (Ps)

* GP2017 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Since the proper name for GP2017 has not yet been determined, the developmental code name, GP2017, is used throughout this review to refer to this product. The proposed proprietary name (Hyrimoz) is only conditionally accepted for this product until the application is approved.

Reference ID: 4314867

Materials Reviewed:

- 12/20/2017, DPMH consult form for proposed adalimumab biosimilar, DARRTS Reference ID 4198471
- 3/9/2018, DPMH review of Humira (adalimumab) injection, BLA 125057. Carrie Ceresa, Pharm D., MPH. DARRTS Reference ID 4231604
- 11/29/2017, DEPI review, Efe Eworuke, Ph.D. DARRTS Reference ID 4187876
- 8/18/2016, DPMH review of AMJEVITA (adalimumab-atto), subcutaneous injection, BLA 761024. Miriam Dinatale, DO. DARRTS Reference ID 3974320[1]
- 9/23/2016, DPMH Addendum to the August 18, 2016 review for AMJEVITA (adalimumab-atto), subcutaneous injection, BLA 761024. Miriam Dinatale, DO. DARRTS Reference ID 3989921[1]
- 3/24/2016, DPMH review of Humira (adalimumab) injection, BLA 125057. Miriam Dinatale, DO. DARRTS Reference ID 3904672[1]
- 3/25/2014, DPMH review of Humira (adalimumab) injection, BLA 125057. Miriam Dinatale, DO. DARRTS Reference ID 3476883[1]

Consult Question: "Please review Section 8 of the proposed labeling"

BACKGROUND

On October 30, 2017, Sandoz Inc., submitted Biologics License Application (BLA) 761071 for Hyrimoz (adalimumab- (b) (4)), which relies upon Humira (adalimumab), BLA 761071, as the reference product. Hyrimoz was originally submitted to the Agency for review on August 25, 2016 but was withdrawn due to inspection issues at one of the proposed manufacturing sites.

- Humira (adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF) and is indicated for the treatment of RA, JIA, PsA, AS, CD, UC, Ps, Hidradenitis Suppurativa (HS) and uveitis (UV). Humira was originally approved in the US on December 31, 2002.
- The reader is referred to the previous DPMH adalimumab reviews indicated above for specific drug characteristics.

DATA REVIEW

The reader is referred to the March 25, 2014, March 24, 2016, August 18, 2016 September 23, 2016, and March 8, 2018 DPMH reviews for adalimumab products and to the November 29, 2017, DEPI review for a detailed data review regarding adalimumab product exposure during pregnancy, lactation and effects on females and males of reproductive potential.

Humira labeling is already in the Pregnancy and Lactation Labeling Rule (PLLR) format. On August 2, 2018, the Humira labeling was further updated with the data from the Organization of Teratology Information Specialists (OTIS) final report from the Humira Pregnancy Registry.

The applicant provided a review and summary of available published literature using PubMed covering the period from April 2016 to January 2018, regarding adalimumab exposure during pregnancy, lactation and females and males of reproductive potential.

Reference ID: 4314867

The literature search revealed 13 articles published since April 2016 regarding the use of adalimumab during pregnancy. For literature from before April 2016, the applicant refers to the September 23, 2016, DPMH review addendum to the August 19, 2016 review for BLA 761024 (AMJEVITA (adalimumab-atto)/Amjevita, Amgen Inc.)

The relevant literature submitted by the applicant is summarized below.

Burmester et al (2017),[2] analyzed data from 15,132 patients exposed to adalimumab products from 28 rheumatoid arthritis clinical trials throughout the globe (including the adalimumab pregnancy exposure registry (APER). Rates of spontaneous abortion and major birth defects were similar between the adalimumab-exposed women and that of unexposed women with RA and healthy women. Rates of preterm births were similar between the adalimumab-exposed and the RA comparison groups.

Lund T and S Thomsen (2016),[3] discussed a total of seven females with psoriasis who were exposed to TNF-inhibitors (a non-US-approved infliximab product and/or a non-US-approved adalimumab product) or to IL12/23 inhibitor ustekinumab during one or more pregnancies. One patient was exposed to adalimumab during two pregnancies at age 25 and 28. Previous drug therapy included topical steroids, methotrexate, ustekinumab, cyclosporine and infliximab. Both pregnancies were successful and full term. One delivery was vaginal and the other cesarean. The patient experienced anemia and elevated liver enzymes (ALP) after birth which was attributed to the pregnancy and not adalimumab exposure.

Kiely et al (2016),[4] includes 21 patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis) exposed to anti-TNF products from 2007 to 2014. During the study period, 18 subjects received anti-TNF products for moderate to severe inflammatory bowel disease (IBD) (47% adalimumab exposed and 53% infliximab exposed). One patient in the adalimumab group experienced a stillbirth at 21 weeks' gestation, following rescue therapy for acute severe ulcerative colitis (ASUC) which occurred 11 days following a colectomy. Twelve subjects were delivered by cesarean section (10 with CD and 2 with UC). Twenty out of 21 subjects delivered a live infant. Two infants had documented low birth weight (<2.5kg), however, neither infant was small for gestational age. There were no major congenital malformations. Five patients were diagnosed with gestational diabetes.

Komoto S et al (2016),[5] discussed a cross-sectional study conducted in Asia to include Japanese women with IBD treated with anti-TNF and/or thiopurines during pregnancy. The following pregnancy exposures were observed: infliximab (n=22), adalimumab

[2] Burmester G et al., 2017, Adalimumab long-term safety: infections, vaccination response and pregnancy outcomes in patients with rheumatoid arthritis, Ann Eheum Dis, 76:414-417.
[3] Lund T and S Thomsen, 2016, Use of TNF-inhibitors and ustekinumab for psoriasis during pregnancy: A patient series, Dermatologic Therapy, 30:e12454.
[4] Kiely CJ et al., 2016, Safe and effective: anti-tumour necrosis factor therapy use in pregnant patients with Crohn disease and ulcerative colitis, Internal Medicine Journal:616-619.
[5] Komoto S et al., 2016, Pregnancy outcome in women with inflammatory bowel disease treated with anti-tumor necrosis factor and/or thiopurine therapy: a multicenter study from Japan, Intest Res, 14:139-145.

(n=2), azathioprine (n=6),6-mercaptopurine (n=1), and infliximab plus azathioprine (n=10). No statistical difference was observed among each group regarding low birth weight, prematurity or congenital anomalies. Spontaneous abortion occurred more frequently in patients treated with anti-TNF's; however, the data were not broken down specifically by individual drug product and too few subjects were exposed to adalimumab to make an adequate conclusion.

Fujikawa et al (2016),[6] reported on a case of a 36-year-old Japanese woman with Behcet's disease (unapproved use) admitted to the hospital with a recurrent ileocecal ulcer. Adalimumab was initiated around gestational week 4 after patient failed treatment with infliximab and was continued until gestational week 20. Disease remission was maintained throughout pregnancy, and the pregnancy was successfully delivered at 37 weeks' gestation and uneventful.

Hoxha et al (2017),[7] discusses 38 prospectively followed pregnancies from 2008 to 2015 exposed to anti-TNF therapy. Approximately 24 patients were exposed to an anti-TNF at conception or during the first trimester, 11 were exposed prior to conception and three were paternal exposures. The women were divided into two group based on exposure timing. Those group are identified as "Group I: exposed to anti-TNFα at conception/1st trimester" and "Group II: exposed to anti-TNFα prior to conception." A total of five women were exposed to adalimumab. One patient who was exposed to adalimumab in group 1 delivered a neonate with a congenital diaphragmatic hernia and obstructive megaureter. Another woman who was exposed to adalimumab also in group 1, delivered her infant at 33 weeks' gestation due to intrauterine growth restriction. More specific data regarding timing of exposure was not available.

The applicant also submitted a summary of reported pregnancies in the clinical studies. Because GP2017 is not yet approved, there are no data in the Pharmacovigilance database; however, there were two pregnancies in study GP17-301. One pregnancy in the adalimumab group was ectopic and the patient underwent laparoscopic salpingectomy. The second patient had a confirmed pregnancy on study week 35 and stopped study drugs on day 133 of the study. The patient delivered a healthy infant at 8 months after study discontinuation without any maternal complications.

DISCUSSION/CONCLUSIONS

The applicant provided an adequate review of literature. The literature review for this memo did not reveal safety concerns regarding pregnancy, lactation or females and males of reproductive potential to be added to labeling. DPMH recommends that adalimumab-(b) (4) labeling is updated to reflect the recent updates to Humira labeling based on the review of the final data from the Organization of Teratology Information Specialists (OTIS) final report from the Humira Pregnancy Registry.

[6] Fujikawa K et al., 2016, Successful Treatment with Adalimumab for Intestinal Behcet's Disease during Pregnancy, Intern Med, 55:1375-1378.

[7] Hoxha A et al., 2017, Pregnancy and foetal outcomes following anti-tumor necrosis factor alpha therapy: A prospective multicenter study, Joint Bone Spine:169-173.

Reference ID: 4314867

RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 in adalibumab- (b) (4) labeling for compliance with the PLLR (see below). DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
Available studies with use of adalimumab during pregnancy do not reliably establish an association between adalimumab and major birth defects. Clinical data are available from the Organization of Teratology Information Specialists (OTIS)/MotherToBaby (b) (4) Pregnancy Registry in pregnant women with rheumatoid arthritis (RA) or Crohn's disease (CD). Registry results showed a rate of 10% for major birth defects with first trimester use of adalimumab in pregnant women with RA or CD and a rate of 7.5% for major birth defects in the disease-matched comparison cohort. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects *(see Data).*

Adalimumab is actively transferred across the placenta during the third trimester of pregnancy and may affect immune response in the *in-utero* exposed infant *(see Clinical Considerations).* In an embryo-fetal perinatal development study conducted in cynomolgus monkeys, no fetal harm or malformations were observed with intravenous administration of adalimumab during organogenesis and later in gestation, at doses that produced exposures up to approximately 373 times the maximum recommended human dose (MRHD) of 40 mg subcutaneous without methotrexate *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S., general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations
Disease-associated maternal and embryo/fetal risk
Published data suggest that the risk of adverse pregnancy outcomes in women with RA or inflammatory bowel disease (IBD) is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Fetal/Neonatal Adverse Reactions
Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester *(see Data).* Risks and benefits should be considered prior to administering live or live-attenuated

vaccines to infants exposed to adalimumab *in utero [see Use in Specific Populations (8.4)]*.

Data

Human Data

A prospective cohort pregnancy exposure registry conducted by OTIS/MotherToBaby in the U.S. and Canada between 2004 and 2016 compared the risk of major birth defects in live-born infants of 221 women (69 RA, 152 CD) treated with adalimumab during the first trimester and 106 women (74 RA, 32 CD) not treated with adalimumab.

The proportion of major birth defects among live-born infants in the adalimumab-treated and untreated cohorts was 10% (8.7% RA, 10.5% CD) and 7.5% (6.8% RA, 9.4% CD), respectively. The lack of pattern of major birth defects is reassuring and differences between exposure groups may have impacted the occurrence of birth defects. This study cannot reliably establish whether there is an association between adalimumab and major birth defects because of methodological limitations of the registry, including small sample size, the voluntary nature of the study, and the non-randomized design.

In an independent clinical study conducted in ten pregnant women with IBD treated with adalimumab, adalimumab concentrations were measured in maternal serum as well as in cord blood (n=10) and infant serum (n=8) on the day of birth. The last dose of adalimumab was given between 1 and 56 days prior to delivery. Adalimumab concentrations were 0.16-19.7 µg/mL in cord blood, 4.28-17.7 µg/mL in infant serum, and 0-16.1 µg/mL in maternal serum. In all but one case, the cord blood level of adalimumab was higher than the maternal serum level, suggesting adalimumab actively crosses the placenta. In addition, one infant had serum levels at each of the following: 6 weeks (1.94 µg/mL), 7 weeks (1.31 µg/mL), 8 weeks (0.93 µg/mL), and 11 weeks (0.53 µg/mL), suggesting adalimumab can be detected in the serum of infants exposed *in utero* for at least 3 months from birth.

Animal Data

In an embryo-fetal perinatal development study, pregnant cynomolgus monkeys received adalimumab from gestation days 20 to 97 at doses that produced exposures up to 373 times that achieved with the MRHD without methotrexate (on an AUC basis with maternal IV doses up to 100 mg/kg/week). Adalimumab did not elicit harm to the fetuses or malformations.

8.2 Lactation

Risk Summary

Limited data from case reports in the published literature describe the presence of adalimumab in human milk at infant doses of 0.1% to 1% of the maternal serum level. Published data suggest that the systemic exposure to a breastfed infant is expected to be low because adalimumab is a large molecule and is degraded in the gastrointestinal tract. However, the effects of local exposure in the gastrointestinal tract are unknown. There are no reports of adverse effects of adalimumab on the breastfed infant and no effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for HYRIMOZ and any potential

adverse effects on the breastfed child from HYRIMOZ or from the underlying maternal condition.

Reference ID: 4314867

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE M CERESA
08/31/2018

MIRIAM C DINATALE
08/31/2018

LYNNE P YAO
09/05/2018

LABEL AND LABELING/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 23, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761071
Product Name and Strength:	Hyrimoz (GP2017) * 40 mg/0.8 mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription
Applicant/Sponsor Name:	Sandoz
FDA Received Date:	October 30, 2017
OSE RCM #:	2016-2029 and 2017-2361
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD
DMEPA Associate Director:	Mishale Mistry, PharmD, MPH
Associate Director for Human Factors:	Quynh Nhu Nguyen, MS

* GP2017 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Since the proper name for GP2017 has not yet been determined, the developmental code name, GP2017, is used throughout this review to refer to this product. The proposed proprietary name (Hyrimoz) is only conditionally accepted for this product until the application is approved.

Reference ID: 4311436

1 REASON FOR REVIEW

This review evaluates the Human Factors study results, proposed carton labeling, container labels, instructions for use (IFU), and prescribing information (PI) submitted on October 30, 2017 for Hyrimoz (GP2017)* Injection (BLA 761071) for areas of vulnerability that could lead to medication errors. Sandoz is seeking licensure for two Hyrimoz presentations: 40 mg/0.8 mL in a single-dose pre-filled glass syringe (with BD UltraSafe Passive™ Needle Guard); and 40 mg/0.8 mL in a single-dose pre-filled pen (Sensoready® Pen).

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested this review to inform their evaluation of the 351(k) BLA submission for Hyrimoz. The reference product, US-licensed Humira (adalimumab) (BLA 125057), was approved on December 31, 2002.

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-N/A
Human Factors Study	C
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other (Information Requests)	F
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our assessment of the Human Factors Validation Results, proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Hyrimoz (GP2017)* injection, BLA 761071 are as follows:

3.1 HUMAN FACTORS

Sandoz has proposed to use the human factors study data gathered for the marketed product, Cosentyx (secukinumab) to apply to the Hyrimoz pre-filled syringe (PFS) and the Hyrimoz Sensoready Pen.

* GP2017 has been developed as a proposed biosimilar to US-licensed Humira (adalimumab). Since the proper name for GP2017 has not yet been determined, GP2017 is used throughout this review in place of the nonproprietary name for this product.

Reference ID: 4311436

Prefilled Syringe Presentation

We also note that the proposed Hyrimoz PFS includes a passive needle guard safety mechanism to prevent needle stick injuries after injection; whereas the US-licensed Cosentyx PFS does not include a needle guard. Therefore, to accurately represent the Hyrimoz PFS, the IFU for the PFS differs slightly from the US-licensed Cosentyx IFU. We find this variation necessary and acceptable. We also note that Erelzi® is provided in the same presentation as the Hyrimoz PFS (i.e. as a prefilled syringe in BD UltraSafe Passive™ Needle Guard). Therefore, we consider that no additional HF studies are needed to support the usability of the Hyrimoz PFS.

Sensoready Pen Presentation

Cosentyx (secukinumab), BLA 125504, is held by Novartis and the Sensoready pen platform was approved as part of this BLA on January 21, 2015. We note that Sandoz is a Novartis company. We also note that, although the proposed Hyrimoz Sensoready pen platform and the marketed Cosentyx Sensoready pen platform are based on the same autoinjector platform, the proposed Hyrimoz Sensoready pen platform contains device differences including the rear end cover, plunger rod, and plunger spring differences:

1. (b) (4)
2. (b) (4)

An information request (see Appendix F), which asked for clarification on how these differences impact usability and the use related tasks, was sent on May 31, 2018. Per Sandoz, (b) (4)

We also note that none of these component changes are visible to the user, however, there is noticeable difference in a lower injection time [range of 4 to 9 seconds (Hyrimoz) compared to 7 to 14 seconds (Cosentyx)] (b) (4). We defer to the CDRH device reviewer to determine the acceptability of the internal component differences from an engineering perspective.

Human Factors Requirements for JIA patients

We also note that the Cosentyx HF validation study did not include a Juvenile Idiopathic Arthritis (JIA) indication. However, Sandoz is proposing the JIA indication for Hyrimoz. An information request (see appendix F) was sent to Sandoz on February 27, 2018 requesting Sandoz to provide a rationale for not including this group of participants as we consider this distinct user group to be part of the intended user population for Hyrimoz.

Upon reviewing the applicant's justification for not including the JIA indication in their HF studies, DMEPA disagrees with the Applicant's justification and we provide our rationale for disagreement below.

1. Sandoz considers JIA and RA to be diseases with the common pathophysiological process of joint involvement and similar clinical signs and symptoms. In terms of cognitive and physical ability, Sandoz notes that the decision for a patient to self-administer Hyrimoz at home is expected to involve the prescribing physician, the healthcare provider (HCP) responsible for training the patient, potential lay caregivers and the patient themselves. Irrespective of whether the patient is an adult with RA or a JIA patient, it is expected that the patient will only self-administer Hyrimoz when willing to do so, having received appropriate training, and having demonstrated the ability to self-inject.

   DMEPA comment: Although prescribers (and parents) are responsible for determining if a pediatric/adolescent patient is able to self-inject after proper training, post-marketing information shows that patients (including pediatric/adolescents) are not always trained in the use of their prescribed medications.

2. In regards to the anthropometric concerns for JIA patients, Hyrimoz has been designed for adolescent and adult users. Consideration was given to the hand size and strength of users with respect to the size and operational forces associated with the user interface of these devices. Critical steps such as removing the cap and pressing the plunger were considered and the force required to perform these tasks fail within the range of abilities for twelve year olds (see Appendix F).

   DMEPA comment: While this data is helpful, clinical disease manifestation alone does not appropriately capture differences between the pediatric population and the adult population that can impact usability.

In summary, DMEPA disagrees with the applicant's justification for not needing HF data in JIA patients. DMEPA considers that HF validation data in JIA patients is necessary to demonstrate safe and effective use of the Hyrimoz Sensoready Pen in pediatric/adolescent patients, taking into account the above considerations and rationale.

3.1 LABELS AND LABELING ASSESSMENT

Reference ID: 4311436

The proposed labels and labeling submitted include: carton labeling, container foil labels, container labels, PI, and IFU. We performed a risk assessment of the submitted labels and labeling for areas of vulnerability that may lead to medication errors.

The Hyrimoz PI closely follows the PI for the reference product, US-licensed Humira (adalimumab). There are differences between the two PIs as Hyrimoz is not indicated for all of the Humira indications (see Appendix A, Table 3). We find the PI acceptable from a medication error perspective and do not have any recommendation.

We also reviewed the IFU, carton labeling, and contain labels and we find them acceptable from a medication error perspective and we have no further recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

We concluded that no additional HF studies are needed to support the usability of the Hyrimoz PFS. With regards to the Sensoready Pen presentation, DMEPA finds no additional HF data is necessary for the adult populations. In addition, we find the proposed carton labeling, container labels, instructions for use, and prescribing information acceptable for the adult populations from a medication error perspective and we have no further recommendations at this time.

With regards to the pediatric/adolescent JIA patients, we disagree with the Applicant's justification for not needing HF validation studies in that patient population for the Sensoready pen presentation. Therefore, we defer to the Division of Pulmonary, Allergy, and Rheumatology Products on appropriate labeling for this user group for the Sensoready Pen presentation.

Reference ID: 4311436

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Hyrimoz received on October 30, 2017 from Sandoz and the reference product.

Table 3. Relevant Product Information for Hyrimoz and the reference product

Product Name	Hyrimoz	US-licensed Humira
Initial Approval Date	N/A	December 31, 2002
Active Ingredient	GP2017*	adalimumab
Indication	• Rheumatoid Arthritis (RA) • Juvenile Idiopathic Arthritis (JIA) (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) (2 years and older) • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Adult Crohn's disease (CD) • Pediatric Crohn's disease (6 years and older) • Ulcerative Colitis (UC) • Plaque Psoriasis (Ps) • Hidradenitis Suppurativa (HS) • Uveitis (UV)
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection	Injection
Strength/How Supplied	40 mg/0.8 mL Prefilled syringe 40 mg/0.8 ml Prefilled pen	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	**Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis:** 40 mg every other week. Some patients with RA not receiving methotrexate may benefit from	**Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis:** 40 mg every week Some patients with RA not receiving methotrexate may benefit from increasing the frequency to 40 mg every week.

	increasing the frequency to 40 mg every week. **Juvenile idiopathic arthritis:** ≥ 30 kg (66 lbs): 40 mg every other week. Healthcare providers should be advised that there is no dosage form for HYRIMOZ that allows weight-based dosing for pediatric patients below 30 kg. Adalimumab products have not been studied in patients with polyarticular JIA less than 2 years of age or in patients with a weight below 10 kg. **Adult Crohn's disease and Ulcerative colitis:** Initial dose (Day 1): 160 mg (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days). Second dose two weeks later (Day 15): 80 mg Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. For patients with Ulcerative Colitis only: Only continue Hyrimoz 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.	**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 Second dose two weeks later (Day 15): 80 mg Two weeks later (Day 29): Begin a maintenance dose of 40 mg every other week. For patients with Ulcerative Colitis only: 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

Reference ID: 4311436

		Third (Day 29) and subsequent doses: 40 mg every week.
Storage	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, 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. Should be discarded if not used within the 14-day period. Record the date when first removed from the refrigerator in the spaces provided on the carton. Do not store in extreme heat or cold.	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, 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. Should be discarded if not used within the 14-day period. Record the date when first removed from the refrigerator in the spaces provided on the carton. Do not store in extreme heat or cold.

APPENDIX C. HUMAN FACTORS STUDY

C.1 Results

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\\cdsesub1\evsprod\bla761071\0005\m3\32-body-data\32r-reg-info\tech-summary-(b) (4)-3.pdf

\\cdsesub1\evsprod\bla761071\0005\m3\32-body-data\32r-reg-info\tech-summary-(b) (4)-4.pdf

APPENDIX F. Information Request

F.1

Dated February 27, 2018

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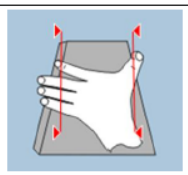
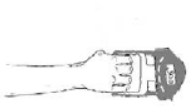
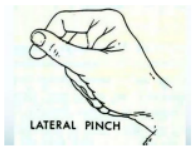
Application 761071 - Sequence 0019 - Response to Request for Information Q1-Q2, dated 27 February 2018

Attribute	Image	Male (percentile)		Female (percentile)	
		5th*	95th	5th	95th
Grip span** [mm] (US)		84 [1]	112 [1]	89 [1]	109 [1]
Grip diameter [mm] (US)		30 [1]	40 [1]	32 [1]	41 [1]
Grip strength [N] (US)		118 [2] 148 [3]	341 [2] 375 [3]	141 [2] 139 [3]	271 [2] 313 [3]
Chuck Pinch strength [N] (US)		42 [2] 43 [3]	106 [2] 95 [3]	38 [2] 49 [3]	102 [2] 88 [3]
Lateral Pinch strength [N] (US)		34 [2] 53 [3]	94 [2] 95 [3]	36 [2] 49 [3]	74 [2] 87 [3]
Pinch pull strength on a 20mm block [N] (UK)		32 [4]	90 [4]	27 [4]	73 [4]

* 5th and 95th percentile values were calculated based on mean and standard deviation.

** No grip span data is available for adolescents, however grip span and grip diameter are closely correlated. The grip span data presented here is calculated as the circumference of the grip diameter multiplied by 0.89, based on the average ratio of grip span to grip diameter in adults.

[1] PeopleSize software, Open Ergonomics Ltd

[2] Ager, C.L., Olivett, B.L. & Johnson, C.L. (1984). Grasp and Pinch Strength in Children 5 to 12 Years Old.The American Journal of Occupational Therapy, 38 (2), 107-113.

[3] Mathiowetz, V., Wiemer, D.M. & Federman, S.M. (1986). Grip and pinch strength: Norms for 6- to 19-year-olds.The American Journal of Occupational Therapy, 40 (10), 705-711.

[4] DTI (2000). *Strength Data for Design Safety - Phase I*. London, UK: URN 00/1070 Department of Trade and Industry.

Dated May 31, 2018

\\cdsesub1\evsprod\bla761071\0030\m1\us\111-information-amendment\rfi16-310518.pdf

Application 761071 - Sequence 0030 - Response to Request for Information, dated 31 May 2018

Reference ID: 4311436

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 Hyrimoz labels and labeling submitted by Sandoz.

- Container label received on October 30, 2017
- Carton labeling received on October 30, 2017
- Container Foil labels received on October 30, 2017
- Instructions for Use received on October 30, 2017
- Prescribing Information (Image not shown) received on October 30, 2017

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

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

Reference ID: 4311436

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/s/

TERESA S MCMILLAN
08/23/2018

SARAH K VEE
08/24/2018

DANIELLE M HARRIS on behalf of MISHALE P MISTRY
08/30/2018

QUYNHNHU T NGUYEN
08/30/2018

OFFICE OF DEVICE EVALUATION

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

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	July 13, 2018
To	Ann-Thy Ly, RBPM and Nina Ton CDER/OPQ/OPRO
Requesting Division	OPQ/OPRO
From	Kathleen Fitzgerald CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	John McMichael, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRRID/GHDB
Subject	Consult for Submission # BLA 761071 ICCR2017-01872 ICC1700894
Recommendation	Device Constituents Parts of the Combination Product are Approvable

Digital Signature Concurrence Table	
Reviewer	Kathleen E. Fitzgerald -S Digitally signed by Kathleen E. Fitzgerald -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0010093027, cn=Kathleen E. Fitzgerald -S Date: 2018.07.13 07:46:49 -04'00'
Team Lead	
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=1300189211, cn=Alan M. Stevens -S Date: 2018.07.17 07:21:12 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	Kathleen Fitzgerald
ICCR SharePoint Link	ICCR2017-01872
ICC tracking # (Lead)	ICC1700894
Submission Number	BLA 761071
Sponsor	Sandoz, Inc
Drug/Biologic	GP2017 (adalimumab, a proposed biosimilar to Humira)
Indications for Use	Rheumatoid Arthritis; Juvenile Idiopathic Arthritis in patients 4 years of age and older; Psoriatic Arthritis; Ankylosing Spondylitis; Adult Crohn's Disease; Ulcerative Colitis; Plaque Psoriasis
Device Constituent	PFS and Autoinjector
Related Files	None listed

Table 2. Review Team				
CDER/CBER Lead Review Division	OPQ/OPRO			
Submission RPM	Ann-Thy Ly, RBPM and Nina Ton, RPM			
Lead Device Reviewer	Kathleen Fitzgerald			
The CDRH review is being managed under ICC #: ICC1700894				
Below is a list of the Discipline Specific ICCR#, ICC# and CON#. The CON# are under ICC1700894 in CTS.				
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**ICCR #**	**ICC #**	**CON #**
Mechanical Engineer	Pete Basile CDRH/ODE/DAGRRID/GHDB	ICCR2018-02210	ICC1700894	CON1813660

Table 3. Important Dates		
Interactive Review Goal Dates		
1st round of Information Requests	March 30, 2018	
2nd Round of Information Requests		
Final Discipline Specific Memos Due	June 15, 2018	
Final Lead Device Review Memo Due	June 28, 2018	
Interim Due Dates	**Meeting Date**	**Due Date**
Filing	N/A	
74-Day Letter	December 11, 2017	
Mid-Cycle	N/A	
Primary Review	June 30, 2018	June 28, 2018
Internal Meeting	N/A	
Safety Meeting	N/A	

Reference ID: 4306205

Sponsor Meeting	N/A	
Written Feedback Due	N/A	
Other		
Other		

TABLE OF CONTENTS

Reference ID: 4306205

2. PURPOSE/BACKGROUND

2.1. Scope

The purpose of this review is for CDRH to review the combination product device constituent's information and performance testing for the PFS and autoinjector.

CDER's request:

Sandoz resubmitted biologic license application (BLA) 761071 on October 30, 2017. This is a 351(k) BLA for approval as a biosimilar to Humira (adalimumab). OPQ is requesting a consult review of the single-dose auto-injector and the pre-filled syringe to determine if the information provided is adequate to support approval of the BLA.

The goal of this memo is to determine if the device constituent's parts of the combination product are approvable. CDRH's review will consist of the device constituent's parts information and performance testing.
CDRH will NOT review the drug product information and testing or human factors review.

2.2. Prior Interactions

Reference ID: 4306205

2.2.1. Related Files

None listed.

2.3. Indications for Use

Combination Product	Indications for Use
GP2017 (adalimumab, a proposed biosimilar to Humira)	Intended for treatment of Rheumatoid Arthritis; Juvenile Idiopathic Arthritis in patients 4 years of age and older; Psoriatic Arthritis; Ankylosing Spondylitis; Adult Crohn's Disease; Ulcerative Colitis; Plaque Psoriasis
PFS and Autoinjector	Delivery of drug product

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Date - Version	Location
BLA 761071	Sequence 0005, 10-30-2017	Global Submit
MAF (b) (4)		Image 2000
IR Quality response	Sequence 0024, 4-18-2018	Global Submit

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

From Section 3.2.P.7 Container closure System

The container closure system for GP2017 40 mg/0.8 mL solution for injection consists of a sterile, non-pyrogenic, single use, pre-filled syringe (PFS) (i.e., (b) (4) prefillable ISO standard glass syringe). The PFS includes the following components:

- A glass syringe barrel with staked needle where the needle is fixed to the syringe barrel
- A rubber plunger stopper
- A rigid needle shield (RNS) composed of a rubber needle shield covered by a rigid shell

The PFS is assembled with either of the following two functional secondary packaging components:

- A plunger rod and a needle safety device (NSD) with an add-on finger flange, as a safety mechanism to reduce occurrence of accidental needle sticks [Module 3.2.R Technical summary needle safety device]
- An autoinjector [Module 3.2.R Technical summary (b) (4) device]

Plunger rod/ NSD and autoinjector are not part of the container closure system (primary packaging) and have no contact with the sterile fluid path.

Table 1 Overview on letters of authorization

Type	Description	Reference #	Supplier
Drug product (DP) primary packaging			
DMF (Section 2) DMF (Section 3) DMF (Section 4)	[redacted] (b) (4)		
Device			
MAF (Section 5)			

2.2 Identity of components and materials of construction

Primary packaging components are constructed of the materials defined in Table 2-1.

Table 2-1 GP2017 40 mg/0.8 mL solution for injection in PFS: Identity of materials of construction

Component	Description	Identity of material	Supplier	Compliance status Ph. Eur./ USP
Syringe with staked needle (sold as sterile and non-pyrogenic)				
Syringe barrel	1 mL long, colorless	[redacted] (b) (4)		Complies with Ph. Eur. and USP requirements for [redacted] (b) (4) glass
Staked hypodermic needle	27 G x 1/2"			
Plunger stopper				
Plunger stopper	Gray rubber stopper Rubber stopper formulation			Complies with Ph. Eur. and USP requirements
Rigid needle shield				
Rigid shell	Plastic shell			Not applicable as not in product contact
Rubber needle shield	Rubber needle shield Rubber formulation			Complies with Ph. Eur. and USP requirements

Picture of GP2017_PFS_[redacted] (b) (4)_40_[redacted] (b) (4) PFS

(b) (4)

GP2017 prefilled syringe (PFS) assembled with a needle safety device (NSD) including an add-on finger flange, which form together a single use combination product. The Sandoz internal code for this combination product used throughout this document is GP2017_PFS_(b) (4)_40_in (b) (4). This combination product is available in one strength, namely:

☐ GP2017 40 mg/0.8 mL prefilled syringe with BD UltraSafe Passive™ Needle Guard (b) (4)

The needle guard assembly is a three-component assembly of a plastic body, plastic guard and metal spring. Once combined with a suitable 1 mL long ISO standard syringe, this needle guard forms an interlocked needle shielding system which allows delivering a medicine in a controlled and safe fashion. The add-on finger flange enlarges the grip area, and thus, provides additional injection support when handling the NSD. The NSD does not come into direct contact with the drug fluid path nor does it provide any protection to the drug product.

Figure 4-1 (b) (4) **Components**

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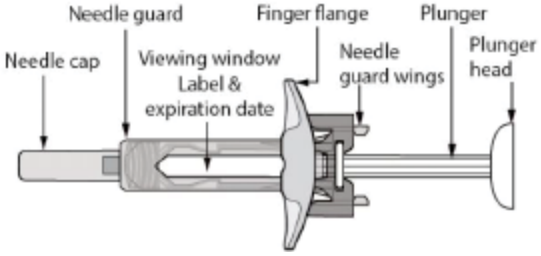
Table 4-1 Applicable documents

Document title	Document code
(b) (4)	

The NSD materials consists of plastic and (b) (4).

Figure 4-2 Schematic figure of the combination product



6.4 Graduation marks and fill line

The product is intended for a single, full dose application. Therefore, there are no graduation marks on the PFS (see [Module 3.2.P.7]) or on the label (see [Module 1.14.1.1]). Also the NSD does not have any graduation or fill marks.

3.2.R (b) (4)-GP2017 40 Autoinjector

The sole function of the (b) (4) AI is to deliver a single, fixed dose, subcutaneous injection of GP20l7. The (b) (4) AT is composed of a main outer body and a prefilled syringe (PFS) carrier assembly inside; the device is spring powered and is designed to administer the entire contents of the PFS in one dose. The (b) (4) AI is not part of the sterile fluid path and does not have any contact with the drug or biologic contained within the prefilled syringe.

(b) (4)

Reference ID: 4306205

Figure 4-1 Composition of (b) (4) -GP2017_40 (exploded view)

(b) (4)

Figure 4-2 Exploded view of front subassembly

(b) (4)

Figure 4-3 Exploded view of rear subassembly

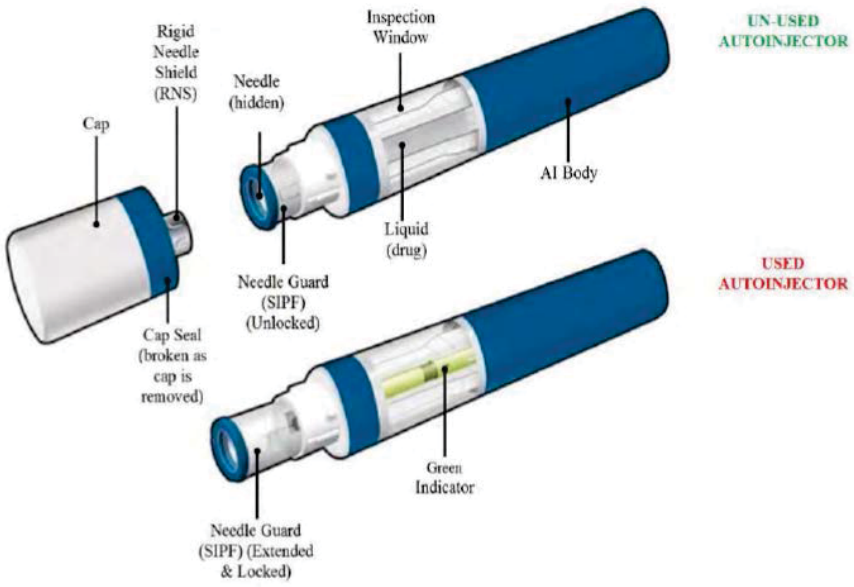
The (b) (4)-GP2017 40 is a single use drug-device combination product consisting of an administration device and a drug product constituent part. The device constituent part is a single-use autoinjector ((b) (4) AI), and the drug component is a 40 mg I 0.8 mL solution of GP2017 provided in a prefilled syringe with a staked needle. The prefilled syringe is assembled into the autoinjector and forms a single unit with the autoinjector which is not to be separated.

The (b) (4)-GP2017 40 is a fixed dose, single dose needle-based injection system with automated functions according to ISO 11608-1 and ISO 11608-5 (see Section 16.1). The corresponding system designation is D1.

The (b) (4)-GP2017 40 consists of the following parts (as shown in Figure 4-4)

- Cap (protects the needle before use)
- Cap Seal (tamper evidence feature)
- Rigid Needle Shield (RNS) (seals the syringe and protects the needle before use) - part of the PFS
- Needle (inserts into the skin)
- Needle Cover (Sharps Injury Prevention Feature (SIPF))
- AI Body (contains the injector mechanism)
- Inspection Window (allows user to check the progress of the injection (green indicator) and check the appearance of the drug before use)
- Green Indicator (shows the progress of the injection as it progresses through the inspection window during injection)

Figure 4-4 Graphical depiction of the (b) (4) GP2017_40 and its key components



See section 10 on steps and instructions on how to use the PFS and AI.

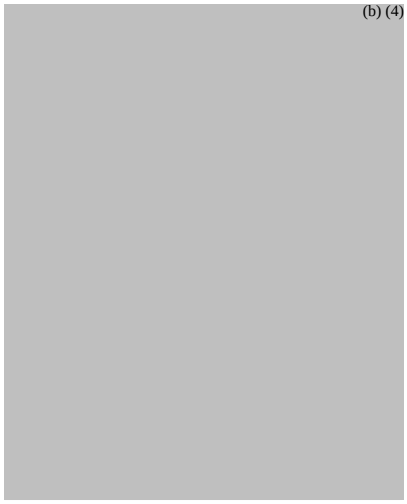
Comparison of the RLD and GP2017 PFS. From IR response dated 4-18-2018

Table 2-1 Comparison of the Humira pre-filled syringe and GP2017_PFS_(b) (4)_40_(b) (4)

Aspect	Humira® PFS	GP2017_PFS_(b) (4)_40 (b) (4)
Device parts		
Syringe	(b) (4) mL long ISO standard glass syringe with staked 27G ½" needle Material: Glass Color: Transparent Dimensions: (b) (4)	(b) (4) 1 mL long ISO standard glass syringe with staked 27G ½" needle. Material: The (b) (4) syringe consist of colorless (b) (4) glass (b) (4) and a staked hypodermic 27G ½" needle (b) (4) glass syringe body. For further details please refer to [Module 3.2.P.7] and the DMF (b) (4) A letter of authorization to the DMF is provided in [Module 1.4.2] Color: Transparent Dimensions: (b) (4)

Aspect	Humira® PFS	GP2017_PFS_(b) (4)_40_(b) (4) (b) (4)
Finger flange	from (b) (4) Material: Plastic Color: Grey Dimensions: (b) (4)	(b) (4) Add-on Finger Flange Material: (b) (4) Color: Beige Dimensions: (b) (4)
Plunger rod	from (b) (4) Material: Plastic Color: (b) (4) Dimensions: (b) (4)	Material: (b) (4) Color: Transparent Dimensions: (b) (4) (b) (4) Plunger Rod
Needle guard	n/a	BD UltraSafe™ Passive (b) (4) needle guard Material: Guard: (b) (4) Body: (b) (4) Spring: (b) (4) Color: Transparent Dimensions: (b) (4)

Aspect	Humira® PFS	GP2017_PFS_(b) (4)_40_(b) (4)
Pictures	(b) (4)	

Syringe label	(b) (4) 
	Syringe label artwork (see [Module 1.14.1.1 Label-GP2017-40-mg-PFS]): (b) (4)  Transparent label material, background prints white, recess of transparent areas As dose setting is not possible with the GP2017 presentations (as described in the product label), no graduation on the label is required.

5. CLINICAL DEVELOPMENT

5.1. Current Study Summary

NO current clinical study.

The Sponsor states in section 1.2 of sequence 0005 that based on the concept of extrapolation of indications, licensure for GP2017 is sought for all indications approved for US-Humira [Module 2.7.3-Table 1-3]. However, at the time of this BLA submission, the indications juvenile idiopathic arthritis in patients between 2 and 4 years, pediatric Crohn's disease, hidradenitis suppurativa, and uveitis are still covered by orphan exclusivity, and therefore they will not be claimed. Consequently, these indications will not be further discussed within this section.
The approach taken by Sandoz is to extrapolate from one product to another by demonstrating that GP2017 and Humira are highly similar in a stepwise approach. Following the FDA guidance Scientific considerations in demonstrating biosimilarity to a reference product (2015) and Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (2015), the scientific justification to support a determination of biosimilarity for each condition of use of the reference product US-Humira is based on the totality of the evidence provided for GP2017.

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

6.1.1. Design 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	X		Attachment 6 - (b) (4) -GP2017_40_URS; Attachment¬ 7¬–¬ (b) (4) -GP2017_40_URS_ (b) (4) For PFS-DMF (b) (4) and (b) (4) 510k (b) (4)
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		Attachment4 -0154-011-VE-T002, (b) (4) GP2017_40_DVERSR_02; Attachment 5 - 0154-011-VE-S002 For PFS-DMF (b) (4) and (b) (4) 510k (b) (4) IR responses, sequence 0024
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		Attachment 3 - (b) (4) -GP2017_40_RA-Ap; (b) (4) -GP2017_40_RMUER_02 PFS-IR response #3
Validation Data • Human factors • Clinical data	X		(b) (4) -GP2017_40_RMUER_02 IR responses, sequence 0024
Traceability Documentation	X		Attachment 9 - (b) (4) -GP2017_40_TRAMA

6.1.2. Design Control Review

The design control can be summarized via a representative screenshot of the traceability matrix ((b) (4) -GP2017_40_TRAMA):

(b) (4)

[redacted]

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

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

Traceability demonstrated for specifications to performance data			

Reviewer Comment:
User Requirements and Traceability documentation are review in Section 4.1.2, under the design control review.

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)	X			Pete Basile	X	
Biocompatibility		X			X	
Sterility			X			
Software / Cybersecurity			X			
Electrical Safety / EMC			X			
Human Factors			X			

*Other discipline specific consults may be necessary based on product characteristics

Standards / Guidance Conformance		**YES**	**NO**	**N/A**
Conformance to Standards	ISO 11608-1:2014 – Needle based injection systems – Requirements and Test Methods	X		
	ISO 11608-2:2012 – Needles	X		
	ISO 11068-4:2006 – Electronic and Electromechanical Pen Injectors			X
	ISO 11608-5:2012 – Automated Functions	X		
Adherence to FDA Guidance	Infusion Pumps Total Product Life Cycle – Guidance for Industry and FDA Staff (2014)			X
	Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	X		
	Guidance for Industry and FDA Staff – Intravascular Administration Sets Premarket Notification Submissions (2008)			X
	Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (2013)	X		
	Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (2002)			X
	Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	X		

	Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)			X

*This table does NOT include discipline specific Guidance / Standards that may be applicable to the review

The following table identifies any standards or relevant FDA guidance documents not listed in the above table that might be referenced by the sponsor or determined to be relevant by the CDRH / ODE reviewer in the course of the design review.

Reference Standard / Guidance	**Description / Extent of FDA Recognition**	**Documentation Adequate**	
		Yes	**No**
Referenced standards not listed in Table above	ISO 10993-1	X	
Reference FDA guidance not listed in Table above			

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9.1 Biocompatibility

The materials of the (b) (4) GP2017_40 fulfill the biocompatibility requirements as defined in ISO 10993-1 (see Section 16.1). Based on the place and time of exposure, the biocompatibility assessment covers the requirements of ISO 10993-5 (in vitro cytotoxicity, see Section 16.1) and ISO 10993-10 (irritation and skin sensitization, see Section 16.1).

For more detailed information and applicable test protocols and report, please refer to the MAF (b) (4) see LoA in [Module 1.4.2]).

Table 9-3 Biocompatibility study documents (generated at (b) (4)

Document title	Document code
(b) (4) MAF (see LoA in [Module 1.4.2]	MAF- (b) (4)
Biocompatibility testing summary	0154-011-TR-S004
Biocompatibility testing summary report for (b) (4)	0154-002-TR-T006

Table 3. Summary of biocompatibility test result

Test performed	Reference standard	FDA Recognition #	Result
Cytotoxicity –MEM Elution Test	ANSI/AAMI/ISO 10993-5:2009	2-153	Pass
Cytotoxicity – MTT Quantitative Evaluation Test	ANSI/AAMI/ISO 10993-5:2009		Pass
Maximization Test for Delayed-Type Hypersensitivity	ANSI/AAMI/ISO 10993-10:2010	2-173	Pass
Skin Irritation Test/ Intracutaneous (Intradermal) Reactivity Test	ANSI/AAMI/ISO 10993-10:2010		Pass

Table 9-5 Overview on patient contacting components and materials for the final combination product

Patient contacting components	Material	Supplier	Biocompatibility	Reference
UltraSafe Passive (b) (4) Needle guard				
Guard Body Spring (no patient contact)	(b) (4)	(b) (4)	Tested according to ISO 10993 - part 5: cytotoxicity - part 10: irritation and sensitization	(b) (4) Table 9-6
(b) (4) Plunger rod				
Plunger rod, clear	(b) (4)	(b) (4)	Tested according to ISO 10993 - part 5: cytotoxicity - part 10: irritation and sensitization	(b) (4) Table 9-6
(b) (4) Add-on finger flange				
(b) (4) Add-on finger flange, beige	(b) (4)	(b) (4)	Tested according to ISO 10993 - part 5: cytotoxicity - part 10: irritation and sensitization	Table 9-6
(b) (4) yringe with staked needle				
Syringe barrel Staked hypodermic needle	(b) (4)	(b) (4)	Tested according to ISO 10993 - part 4: haemocompatibility - part 5: cytotoxicity - part 10: irritation and sensitization - part 11: systemic toxicity and pyrogenicity	DMF- (b) (4)

Patient contacting components	Material	Supplier	Biocompatibility	Reference
Rigid needle shield				
Rigid shell	(b) (4)	(b) (4)	Tested according to ISO 10993 - part 5: cytotoxicity - part 10: irritation and sensitization	DMF (b) (4)
Rubber needle shield			Tested according to ISO 10993 - part 4: haemocompatibility - part 5: cytotoxicity - part 10: irritation and sensitization - part 11: systemic toxicity and pyrogenicity	DMF

Reviewer Comments: The biocompatibility data and test reports are adequate for the PFS and autoinjector skin contact, short duration.

7.2. Design Validation Review

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

7.3. Design Verification Review

Overview of the Design Verification tests completed and document number/location

Table 3-1 Design verification documents (b) (4) GP2017_40

Document Title	Document No.	Version
Justification of test items for Design Verification of GP2017-(b) (4)40	0154-011-OT-S008	2.0
Packaging verification		
Design Verification Test Protocol – Packaging	(b) (4) GP2017_40_DVERP_Packaging	01
Design Verification Test Report – Packaging	(b) (4) GP2017_40_DVERR_Packaging	01
Biocompatibility		
(b) (4)		2013-10-15 2014-07-22
Biocompatibility Testing Summary	0154-011-TR-S004	2.0
Biocompatibility Testing Summary Report for (b) (4)	0154-002-TR-T006	1.0
Stability		
Aging Test Report (Durability test) for (b) (4)	0154-004-ATR-T001	A
Risk Assessment for (b) (4) storage conditions	0154-002-RM-S010	2.0

Document Title	Document No.	Version
Risk Assessment for GP2015-(b) (4)50 and GP2017-(b) (4)40 Storage Conditions	0154-010-RM-S008	2.0
Justification Memorandum for (b) (4) Storage Condition – (b) (4)	0154-004-OT-T139	2.0
Transport verification		
Transportation Test Protocol for (b) (4) (b) (4)	0154-002-TTP-0001	1.0
Transportation Test Report For (b) (4) (b) (4)	0154-002-TR-T001	1.0
Transportation Test Protocol for GP2017 (b) (4)	0154-011-TP-T003	2.0
Transportation Test Report for GP2017 (b) (4)	0154-011-TR-T003	2.0
Design Verification		
Design Verification Plan	(b) (4)GP2017_40_DVERPL_01	01
Design Verification Test Protocol for GP2017-(b) (4)40	0154-011-TP-T002	1.0
Design verification protocol for Assessment by project team for GP2017-(b) (4)40	0154-011-VE-S002	1.0
Vibration Test Report for (b) (4)	0154-002-VTR-0001	1.0
Design Assessment Test Report for GP2017-(b) (4)40	0154-011-TR-T001	1.0
Design Verification Test Report for the (b) (4)02A Device	0154-004-DVTR	3.0
Design Verification Test Report for GP2017-(b) (4)40	0154-011-TR-T002	1.0
Design Verification Summary Report	(b) (4)GP2017_40_DVERSR (this document)	02

Document Title	Document No.	Version
Design Verification Master Report	0154-011-VE-T002	1.0
Process Validation Activities		
Process Validation Master Plan	VMP-0154-011	1.0
Process Validation Master Report	VMR-0154-011	2.0

A significant portion of the design verification testing was not completed on the final, finished design of the device. MAF (b) (4) states the following with regards to the different device designs:

"For clarification, (b) (4) would like to point out that these three injectors, (b) (4) (0154-002), (b) (4) (154-004) and GP2015-(b) (4) 50-(0154-010), utilizes the same device design, the only difference is the pharmaceutical drug/syringe content. The GP2017-(b) (4)-40 Autoinjector utilizes the same common components as the other (b) (4) devices [((b) (4) (0154-002), (b) (4) (154-004) and GP2015-(b) (4) 50-(0154-010)], except for three components.

The three different components are the Rear end cover, Plunger rod and Plunger spring. The differences are 1) (b) (4) and 2) (b) (4) . The function of the revised spring, Plunger rod and Rear end cover are identical to the same components used in other (b) (4) devices."

The components of the multiple (b) (4) devices are compared in the table below:

Product name	(b) (4)		GP2015-(b) (4)50	GP2017-(b) (4)40
Project code	0154-002	0154-004	0154-010	0154-011
Needle cover extension	Same	Same	Same	Same
Actuator Sleeve				
Syringe Driver				
Needle Cover				
Syringe Carrier				
Front End Cover				
Syringe Collar				
Actuator				
Front Shell				
Cap (b) (4)				

Spring Guide Rod				
Needle Cover Spring				
Shield Remover				
Rear End Cover				Different
Plunger Rod				Different
Plunger Spring				Different

Table 9-1 Performance requirements of (b) (4) GP2017_40

Design Input	Performance Requirement	Test Item	Test Method	Acceptance Criteria	Results
DIR 4.1	The injection time into air shall be less than or equal to (b) (4) seconds.	Injection time	Measure the time required for a device to expel the drug contents completely from the starting point to the completion point of the injection. This is measured by a detailed video camera recording system	(b) (4)	PASS
DIR 4.2	The delivered volume shall be equal or larger than (≥) (b) (4) mL calculated according to the dose accuracy requirement specified in ISO 11608-1 (D1, N=60, one side tolerance limit factor k at 95% CI with 0.975P)	Dose accuracy	Weight the mass expelled from the PFS to ensure that the drug was expelled completely during injection. Gram is converted into ml and a micro-balance scale is used for measurement. Record the value. The method is aligned with ISO 11608-1:2012.		PASS
DIR 4.3	The needle injection depth shall be (b) (4) mm	Injection depth	Measure the Needle length exposed during injection through a detailed video camera recording system. Record the distance value.		PASS
DIR 4.4	The displacement of the Needle cover before activation shall be between (b) (4) mm (b) (4) mm (excluding initial play)	Needle cover displacement at activation	When the activation force is measured, the Needle cover displacement length is also measured in the tensile testing system		PASS
DIR 4.5	The activation shall occur at a minimum distance of (b) (4) between the Needle cover extension and the Front end cover	Activation point inspection	Hold the autoinjector vertically by hand with a standard distance gauge placed perpendicularly against the length of the Needle cover. Replace the gauge with shorter gauges until activation. When activated, record the value of the gauge between the Needle cover extension and the Front end cover		PASS
DIR 4.6	The needle point shall be at least (b) (4) mm inside the edge of the needle cover after completed injection, when the Needle cover is exposed to a force of, at least, (b) (4) N	Needle cover distance	Expose the Needle cover to (b) (4) N followed by measurement of the distance between the Needle tip and the outer edge of the Needle cover extension with a digital meter indicator. According to ISO 11608-5:2012		PASS
DIR 4.7	The force on the Needle cover to trigger activation shall be between (b) (4) and (b) (4)	Activation force	Measure the force applied on the Needle cover to trigger activation through a tensile testing system. Record the force value.		PASS

Design Input	Performance Requirement	Test Item	Test Method	Acceptance Criteria	Results
DIR 4.8	The Needle cover override force after injection shall be at least (b) (4) N (instantaneous) with less or equal to (≤) (b) (4) mm displacement of the Needle cover	Needle cover safety, displacement at (b) (4) N	Verify by length that a force of ≥ (b) (4) N cannot push the Needle cover back into the Front subassembly after injection, and that the needle cannot be seen after the Needle cover withstood (b) (4) N. Test performed with fixture and tensile testing system.	(b) (4)	PASS
DIR 4.9	The separation force between Front shell and Rear end cover shall be at least (b) (4) N	Rear end cover and Front shell separation force	Assemble the Rear end cover and Front shell. Activate the load-cell on the tensile testing system and separate the Rear end cover and the Front shell. Record the maximum force value when they are separated.		PASS
DIR 4.10	The separation force between the Front shell and Front end cover shall be at least (b) (4) N	Front end cover and front shell separation force	Assemble the Front end cover and the Front shell. Activate the load-cell on the tensile testing system and separate the Front end cover and the Front shell. Record the maximum force value when they are separated.		PASS
DIR 4.16	The separation force between the Cap and the RNS remover shall be (b) (4) N	Cap and RNS remover separation force	Assemble the Cap and Shield remover. Activate the load-cell on the tensile testing system and separate the Shield remover from the Cap. Record the maximum force value when they are separated.		PASS
DIR 4.17	The separation force between the RNS remover and the RNS shall be (b) (4) N	Shield remover and RNS separation force	Assemble the Shield remover and a RNS (rigid needle shield) of the syringe. Activate the load-cell on the tensile testing system and push out the RNS from the Shield remover. Record maximum force value when they are separated.		PASS
DIR 4.20	The rotation torque should be (b) (4) Nm when twisting off the Cap from device with label	Cap removal torque	The torque fixture is attached on the digital torque meter and the final assembled device with label is attached onto the fixture. Then the peak torque needed to separate Cap and Shield remover from the device is recorded.		PASS
DIR 4.21	The separation force between the Cap and the Front end cover (plastic parts only) shall be (b) (4)	Cap pull off force from front end cover	Assemble the Cap, the Front end cover and the Front shell. Activate the load-cell to separate the Cap from Front end cover axially. Record the maximum force value when they are separated. (Plastic parts only).		PASS

Design Input	Performance Requirement	Test Item	Test Method	Acceptance Criteria	Results
DIR 4.25	The overall weight of the device, including filled 1 ml syringe, must not exceed (b) (4)	Total weight	After assembling the Syringe into the autoinjector, weigh the assembled device on the microbalance scale and record the value.	(b) (4)	PASS
DIR 4.26	Total length: (b) (4) mm Cap length: (b) (4) mm Max diameter (b) (4) mm	Injector measurement	Dimension measurement of autoinjector outer dimensions with 2D vision measurement machine.		PASS
DIR 4.11	The device shall give an audible feedback at the start of the injection stroke	Attribute Test	Remove the Cap manually from the autoinjector. Hold the device vertically against the injection pad and lower it (i.e. depress the Needle cover) manually until activation. After the activation when the autoinjector left the pad, control that the Needle cover can't be pushed back into the autoinjector manually.		PASS
DIR 4.12	The device shall give an audible feedback signaling "end of injection" as late in the injection stroke as practically possible	Attribute Test			PASS
DIR 4.13	The device shall have a visible end of injection indicator	Attribute Test	During injection, items as described in column 'acceptance criteria' are checked.'		PASS
DIR 4.14	It shall be possible to monitor the Plunger rod movement during the injection stroke	Attribute Test			PASS

The following functional/performance requirements can be found in MAF (b) (4):

2.1 Functional/Performance Requirements (Ambient Conditions: 18°- 28℃, 25%-75% RH)

DIR Item No.	Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
4.1	The injection time in air shall be less than or equal to (≤ (b) (4) seconds.	4.1	Yes	N/A
4.2	The delivered volume shall be equal or larger than (≥ (b) (4) ml calculated according to the dose accuracy requirements specified in ISO11608-1 ((D1, N=60, one side tolerance limit factor k at 95% CI with 0.975 P).	4.2	Yes	

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The needle injection depth shall be (b) (4) mm.	4.3	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The displacement of the Needle Cover before activation shall be between (b) (4) mm (excluding initial play).	4.4	No	
The activation shall occur at a minimum distance of (b) (4) mm between the Needle cover extension and the Front end cover.	4.5	No	
The needle point shall be at least (b) (4) mm inside the edge of the needle cover after completed injection, when the Needle Cover is exposed to a force of, at least, (b) (4) N.	4.6	No	
The force on the Needle cover to trigger activation shall be between (b) (4) (b) (4)	4.7	No	
The Needle Cover override force after injection shall be at least (b) (4) N (instantaneous) with less or equal to (≤) (b) (4) mm displacement of the Needle Cover.	4.8	No	
The separation force between Front Shell and Rear end Cover shall be at least (b) (4) N (Typical value (b) (4) N).	4.9	No	
The separation force between Front Shell and Front end Cover shall be at least (b) (4) N.	4.10	No	
The device shall give an audible feedback at the start of the injection stroke.	4.11	Yes	See Note 1
The device shall give an audible feedback signalling "end of injection" as late in the injection stroke as practically possible.	4.12	Yes	
The device shall have a visible end of injection indicator.	4.13	Yes	
It shall be possible to monitor the Plunger Rod movement during the injection stroke.	4.14	Yes	

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The device shall allow for visual inspection of the drug product, i.e. the formulation and the pre-filled syringe.	4.15	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The separation force between the Cap and the RNS Remover shall be ≥ (b) (4) N.	4.16	No	
The separation force between the RNS Remover and the RNS shall be ≥ (b) (4) N.	4.17	No	Identical device components and syringe components are used
When the Cap is twisted off from the device, any potential rotation of the RNS may not cause coring (cut out of rubber particles).	4.18	No	
The needle must be hidden before use.	4.19	Yes	See Note 1
The rotation torque should be ≤ (b) (4) Nm when twisting off the Cap from device with label.	4.20	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The separation force between the Cap and the Front end cover (plastic parts only) shall be (b) (4) (b) (4)	4.21	No	
The noise level and tactile response during activation and injection shall be acceptable by the customer.	4.22	Yes	See Note 1
The syringe needle shield must not be moved outwards from the syringe during handling/assembly in a way that the needle is exposed to microbiological contamination.	4.23	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The assembly of the PFS must be facilitated by sufficient guiding and chamfers in Front sub-assembly.	4.24	No	
The overall weight of the device, including filled 1 ml syringe, must not exceed (b) (4)	4.25	Yes	N/A

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The device shall be free from visual and functional defects after vibration testing according to ISO 11608-1:2012.	4.37	No	This property is not influenced by the difference of the 3 components and pre-filled syringe
Front subassembly: Cap (b) (4) (b) (4) Needle cover extension (b) (4) Front end cover (b) (4) Rear subassembly: Plunger rod (b) (4) Rear end cover (b) (4)	4.38	Yes	See Note 1
The cap must be designed to prevent accidental activation when removed and the user must not be able to activate the device without removing the cap.	4.39	Yes	

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
Total length: (b) (4) mm. Cap length: (b) (4) mm Max diameter (b) (4) mm	4.26	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The device must automatically insert the needle and inject the medication.	4.27	Yes	See Note 1
The design of the device shall be adopted for delivery of one dose with Pre filled syringe fill volume lower than (b) (4) ml.	4.28	No	
The device must comprise no more than two sub-assemblies that are to be assembled with the pre-filled syringe in a final assembly step.	4.29	Yes	
The device must have a triangular cross section, as described in the Industrial design report.	4.30	Yes	
The outer shape of the device must not have any sharp edges.	4.31	Yes	
The body of the device must have a straight shape, without curves.	4.32	Yes	
The device must be actuated by pressing the needle cover against the injection site only, without additional trigger button.	4.33	Yes	
The device must have a protective Cap, to be removed prior to injection.	4.34	Yes	
The Cap must be possible to remove by a rotational movement, using a cam curve as described in Industrial design report.	4.35	Yes	
The device must have a needle cover that locks in its outer position, protecting the needle, after injection.	4.36	Yes	

2.3 Usage and durability requirements

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The shelf life of components shall be at least (b) (4) years when stored in temperatures between (b) (4)	8.1	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content. The design differences compared to GP2015 (b) (4) are: 1. Plunger spring 2. Plunger Rod 3. Rear End Cover. The Plunger spring was subject to all relevant durability tests in the course of (b) (4) (refer to test report#0154-004-ATR-T001). The Plunger Rod and Rear End Cover have only been changes regarding (b) (4) The material is identical to (b) (4) which has also been subject to all relevant durability tests (refer to test report ##0154-004- ATR-T001). It is considered that the (b) (4) (b) (4) has no impact on the durability of the device. Consequently the durability requirements #0154-011-IR-S003 Rev 1.0 are considered covered by test report #0154-004- ATR- T001)
The shelf life of front and rear subassembly shall be at least (b) (4) years when stored in temperatures between (b) (4) (b) (4)	8.2	No	
The shelf life of the assembled device shall be at least (b) (4) years when stored in temperatures between (b) (4)	8.3	No	

Additional Verification data referenced in MAF performed by Sandoz: *[Module 3.2.R Technical summary (b) (4) device - Attachment 4]*

1) Final device functional test (b) (4)

Item	Test Name	Output/ unit	DIR item (0154-011-IR-S003r1.0)	Testing instruction	Specification limit	Amounts
Test 1	Injection time	sec.	#4.1	0154-002-TI-F013r4.0	The injection time in air shall be less or equal to (≤) (b) (4) seconds.	60pcs (with label)
	Dose accuracy	ml	#4.2		The delivered volume shall be equal or larger than (≥) (b) (4) ml calculated according to the dose accuracy requirements specified in ISO11608-1 ((D1, N=60, one side tolerance limit factor k at 95% CI with 0.975P)	

Statistical Value	Injection Time (sec.)	Dose Accuracy (ml)
Mean	*4*	*0.817*
Max.	*5*	*0.828*
Min.	*3*	*0.787*
StDev.	*0.49*	*0.0074*
Result	*PASS*	*0.817-(2.384*0.0074)=0.799≥* (b) (4) *ml PASS*

2) Drop test (T=23±5℃, RH: 50±25%)

Item	Test Name		Output / unit	DIR item (refer to 0154-011-OT-S008r1.0)	Test instruction	Specification	Amounts
Test 2	Three directions	Visual inspection	Pass/ Fail	#7.2	ISO 11608-1:2012	The device shall be free from visual and functional defects after (b) (4) mm free fall testing.	60pcs (with label)
		Dose accuracy	ml		0154-002-TI-F013r4.0	➢ Each data must fulfil $\bar{x}$-(k*s) ≥ (b) (4) ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.950P. ➢ $K_{act} \geq k$	
		Injection time	sec.			≤ (b) (4) (All individual value within this limit)	

Visual Inspection After Drop Test	
Horizontal Direction	PASS
Cap Upward Direction	PASS
Cap Downward Direction	PASS

Horizontal Direction		
Statistical Value	Dose Accuracy (ml)	Injection Time (sec.)
Mean	*0.813*	*4*
Max.	*0.821*	*4*
Min.	*0.796*	*3*
StDev.	*0.0069*	*0.32*
Result	*0.813-(2.396*0.0069)=0.796≥* (b) (4) *ml* (b) (4) *(PASS)*	*PASS*

Cap Upward Direction		
Statistical Value	Dose Accuracy (ml)	Injection Time (sec.)
Mean	*0.815*	*4*
Max.	*0.824*	*4*
Min.	*0.803*	*3*
StDev.	*0.0060*	*0.40*
Result	*0.815-(2.396*0.0060)=0.801≥* (b) (4) *ml* (b) (4) *(PASS)*	*PASS*

Cap Downward Direction		
Statistical Value	Dose Accuracy (ml)	Injection Time (sec.)
Mean	*0.811*	*4*
Max.	*0.821*	*4*
Min.	*0.792*	*3*
StDev.	*0.0065*	*0.35*
Result	*0.811-(2.396*0.0065)=0.795≥* (b) (4) *ml* (b) (4) *(PASS)*	*PASS*

3) Environmental requirements

Item	Precondition and testing at	Test Name	Output/ unit	DIR item (refer to 0154-011-OT-S008r1.0)	Test instruction	Specification	Amounts
Test 3	Injection shall be completed in cool atmosphere (5±3℃).	Dose accuracy	ml	#7.6	ISO 11608-1:2012, 0154-002-TI-F002r02	➢ Each data must fulfil $\bar{x}$-(k*s) ≥ (b) (4) ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.975P. ➢ $K_{act} \geq k$	60pcs
	Injection shall be completed in warm atmosphere (40±2℃, 50±10%RH).			#7.7			60pcs

Statistical Value	Injection at Cool (5±3℃)	Injection at Warm (40±2℃, 50±10%RH)
	Dose Accuracy (ml)	Dose Accuracy (ml)
Mean	*0.821*	*0.811*
Max.	*0.835*	*0.823*
Min.	*0.801*	*0.788*
StDev.	*0.0091*	*0.0067*
Result	*0.82-(2.384*0.0091)=0.799≥* (b) (4) *ml* (b) (4) *PASS*	*0.811-(2.384*0.0067)=0.795* (b) (4) *ml* (b) (4) *PASS*

4) Storage environmental test

Item	Precondition	Test Name	Output / unit	DIR item (refer to 0154-011-OT-S008r1.0)	Test instruction	Specification	Amounts
Test 4	Injection shall be completed after subassemblies have been preconditioned for 96hours at 55±2℃ (50±10%RH).	Dose accuracy	ml	#7.3	ISO 11608-1:2012, 0154-002-TI-F002r02	➢ Each data must fulfil $\bar{x}-(k*s) \geq$ (b) (4) ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.975P. ➢ $K_{act} \geq k$	60pcs
	Injection shall be completed after subassemblies have been preconditioned for 96hours at -40±3℃.			#7.4			60pcs
	The sub-assemblies shall be free from visual and functional defects after cyclical preconditioning. (variant 1, 6 cycles and upper temperature 55±2℃)	Visual inspection	Pass/ Fail	#7.5	The sub-assemblies shall be free from visual and functional defects after cyclical preconditioning		60pcs
		Dose accuracy	ml		ISO 11608-1:2012, 0154-002-TI-F002r02	➢ Each data must fulfil $\bar{x}-(k*s) \geq$ (b) (4) ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.950P. ➢ $K_{act} \geq k$	

Statistical Value	Preconditioning after 55±2℃, 50±10%RH	Preconditioning after -40±3℃
	Dose Accuracy (ml)	Dose Accuracy (ml)
Mean	*0.821*	*0.821*
Max.	*0.833*	*0.832*
Min.	*0.796*	*0.801*
StDev.	*0.010*	*0.0069*
Result	*0.821-(2.384*0.010)=0.797≥* (b) (4) *ml* (b) (4) *PASS*	*0.8-(2.384*0.0069)=0.805≥* (b) (4) *ml* (b) (4) *PASS*

Statistical Value	Cyclical Preconditioning
	Dose Accuracy (ml)
Mean	*0.815*
Max.	*0.831*
Min.	*0.797*
StDev.	*0.0076*
Result	*0.815-(2.022*0.0076)=0.800≥* (b) (4) *ml* (b) (4) *PASS*

Item	Test Name	Output/ unit	DIR item (refer to 0154-011-OT-S008r1.0)	Test instruction	Specification	Amounts
Test 5	Package inspection	Pass/ Fail	#7.1	ASTM D4169-09	Refer to Note	2 cartons
	Product inspection					658pcs
	Dose accuracy	ml		0154-002-TI-F002r02	➢ Each data must fulfil $\bar{x}$-(k*s) ≥ (b) (4) ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.975P. ➢ K… >k	30pcs
	Injection time	sec.			(b) (4) (All individual value within this limit)	

Package and Product Inspection		
Based on the inspection, the carton is still intact and there is no any defect on the tray and sample. Therefore, the package and product inspection are PASS.		
Statistical Value	Dose Accuracy (ml)	Injection Time (sec.)
Mean	*0.812*	*4*
Max.	*0.825*	*4*
Min.	*0.795*	*3*
StDev.	*0.0069*	*0.36*
Result	*0.812-(2.608*0.0069)=0.794≥* (b) (4) *ml* (b) (4) *PASS*	*PASS*

The Sponsor has additional adequate verification test reports and results for the PFS and safety device in the IR responses 1-6 of this memo.

Reviewer Comment:
The verification testing provided is acceptable to ensure that the PFS and safety device and (b) (4) _GP2017_40 autoinjector meets its essential performance requirements when delivering the GP2017 drug in its intended use environment.

The sponsor provided appropriate justifications when using the (b) (4) or (b) (4) -40 autoinjector devices.

8. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

8.1. Discipline 1 Mechanical Engineer review of pen injector

Please see attached full consult memo for details. Parts of the consult memo review have been incorporated into the lead reviewer memo.

9. RISK ANALYSIS

9.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		

9.2. Summary of Risk Analysis

Reference ID: 4306205

Table 3-2 Risk analysis, risk evaluation and risk control documents

Document Title	Document No.
Hazard Identification List	(b) (4) GP2017_40_HID
Hazard Identification Checklist (b) (4)	0154-011-RM-S003
Application/Usability Risk Assessment	(b) (4) -GP2017_40_RA-Ap
Application Specification	-GP2017_40_ASPEC
Usability Specification	-GP2017_40_USPEC
Primary Operating Functions	-GP2017_40_POF
Design FMEA (b) (4)	0154-011-RM-S002
Process FMEA SKD 2 (b) (4)	GP2017- (b) (4) -40 SKD2 SAAM FMEA-0154K-E001
Process FMEA SKD 3	(b) (4) 02B SKD3 SAAM FMEA-0154G-E002
Process FMEA SKD 4	(b) (4) 01A SKD4 SAAM FMEA-0154B-E010
Process FMEA SKD 5	(b) (4) 01A SKD5 SAAM FMEA-0154B-E009
Process FMEA SKD 6 SAAM1 (b) (4)	(b) (4) SKD6 SAAM FMEA-0154B-E005 (b) (4)
Process FMEA SKD 6 SAAM2	(b) (4) SKD6 SAAM FMEA-0154B-E007 (b) (4)
Process FMEA SKD 6 SAAM3	(b) (4) SKD6 SAAM FMEA-0154B-E014 (b) (4)
Process FMEA (b) (4) product assembly (clinical batch)	(b) (4) GP2017_40_RA-PR
(b) (4) Auto-Injector Assembly Process FMEA (b) (4) (b) (4)	RA-140-101-15-12-001
(b) (4) Auto-Injector Assembly Process FMEA Summary Report (b) (4)	RA-140-101-15-12-003
Risk Estimation & Evaluation Report (b) (4)	0154-011-RM-S004

Table 3-5 ALARP risks from the usability risk assessment

Risk category	Related Risks	Current Controls	Risk/Benefit
Accidental needle stick due to mishandling of the device	0.25; 2.01; 4.15; 4.16; 6.17; 0.26; 2.02; 4.17; 4.25; 5.10; 9.03	Design: the needle is mechanically protected before and after injection, exposure time is minimal. Design of the package to improve device protection; IFU provides information for safety on how to store, handle and dispose of the device.	Risks associated with a needle stick are well known, however those risks were evaluated considering indication and drug specific aspects and shown that benefit of using a needle based device for subcutaneous injections outweighs potential risks associated with it due to low probability of occurrence.
Swallowing of small components	0.23; 4.13; 4.14; 4.28; 9.01; Other 3	IFU instructs how to dispose of the device and how to store the device out of reach of children	Users are trained per the instructions of the IFU on how to store and dispose of the product Also, the use of the proposed device for injection will not significantly increase the likelihood of choking hazard due to long chain of events that need to occur in parallel which reduces the probability of occurrence.
Mismatch between the drug and the patient (i.e. injection to incorrect patient or injection of a wrong drug) due to mix-up	5.14; Other 2	IFU provides information for safety about the drug	These risks are common in the environment where any drug is used and they are independent on drug representation and/or used device. The benefit of patient treatment outweighs the risk of mix-up.
Accidental injection to a child	0.22; 4.20	IFU instruct show to store device out of reach of children	Considering the long chain of events that would be required to results in an injection to a child, the probability of this occurrence is very low to low. Consequently, the risk management team deems the benefits of using the Delta autoinjector for s.c. injections to outweigh the risks.

Risk category	Related Risks	Current Controls	Risk/Benefit
Potential infection due to microbial contamination related to the device (e.g. impaired device integrity due to mishandling)	0.28; 1.12; 3.01; 3.02; 4.11; 4.18; 4.23; 5.09; 5.15; 8.04; 8.05	Design of the package to improve device protection; IFU instructions show how to use the device.	Risks of microbial contamination through subcutaneous injection are well known and it is commonly acknowledged that these risks cannot be fully excluded despite implementation of appropriate mitigations. However, those risks were evaluated considering disease specifics, intended users' population and environment in which the drug administered. The risk management team deems that the risk of contamination is outweighed by benefits of subcutaneous injection.
Improper storage/ handling	1.07; 6.10	IFU provides information on storage conditions IFU instructions show how to use the device.	Users are trained per the instructions of the IFU on how to store and handle the product. This outweighs all risks related to incorrect storage.
Transfer of transmissible diseases	0.34; 6.05; 9.02; 9.04	Design: Needle guard protects the needle after injection; IFU instructs how to dispose of the device safely.	Risks associated with transfer of transmissible diseases via needle stick are well known for needle based injection systems. However those risks were evaluated considering disease specifics and intended users' population. There are two means of needle protection after injection: by the needle guard and by sharps container reducing the probability of a needle stick to a low occurence. Therefore, the benefit of using a needle based device for injections outweighs potential risks associated with its use.

Risk category	Related Risks	Current Controls	Risk/Benefit
Incorrect dosage due to misunderstanding and/or mishandling	7.04; 8.03; Other 4; Other 5; 6.04; 5.19; 6.23; 1.03; 5.13; 5.20; 6.06; 7.01; 6.03; 5.18; 6.13; 6.22	Design: fixed dose device IFU provides information about the dosage and instructs how to handle the device	Users are trained per the instructions of the IFU and the device design is based on a fixed dose to minimize the risks of incorrect dosage. No dose setting is possible. The benefit of patient treatment outweighs the residual risk of incorrect dosage.
Allergic reaction to device materials	6.15; 7.03; 7.06; 7.08;	Design:The materials used for the (b) (4) autoinjector fulfill the biocompatibility requirements of ISO 10993	Current risk control limits the number of used materials and excludes use of bio incompatible materials. However there is a chance that some of the users have an allergy to selected materials. This risk cannot be completely excluded and risk management team deems that this risk has been reduced to an acceptable level and benefits outweigh the risk.
Improper activation or removal of device	4.26; 5.11; 6.19; 7.02	IFU instructions show how to use the device..	Users are trained per the instructions of the IFU. This risk cannot be completely excluded and risk management team deems that this risk has been reduced to an acceptable level and benefits outweigh the risk.

Located in IR response to PFS question 3 under sequence 003, Sandoz has submitted the GP2017_PFS_(b)(4)_40_in (b) (4) risk management and usability engineering report (see [Attachment 1 - GP2017_PFS_(b)(4)_40_in (b) (4) RMUER]), providing an overview over performed risk management activities as well as the results. In addition, the GP2017_PFS_(b)(4)_40_in (b) (4) usability risk assessment (see [Attachment 2 -

GP2017_PFS_[redacted]_40_in[redacted]_RA-Ap]), which evaluates the risk an end user faces when using the GP2017_PFS_[redacted]_40_in[redacted] combination product by following the Instructions for Use is being submitted.

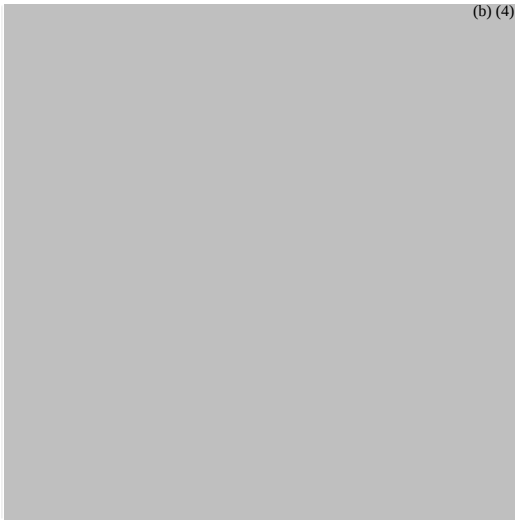
The sponsor provided the following table with regards to the risk analysis activities for the autoinjector:

Table 3-2 Risk analysis, risk evaluation and risk control documents

Document Title	Document No.
Hazard Identification List	[redacted]GP2017_40_HID
Hazard Identification Checklist [redacted]	0154-011-RM-S003
Application/Usability Risk Assessment	[redacted]GP2017_40_RA-Ap
Application Specification	GP2017_40_ASPEC
Usability Specification	GP2017_40_USPEC
Primary Operating Functions	GP2017_40_POF
Design FMEA [redacted]	0154-011-RM-S002
Process FMEA SKD 2 [redacted]	GP2017-Delta-40 SKD2 SAAM FMEA-0154K-E001
Process FMEA SKD 3	[redacted]_02B SKD3 SAAM FMEA-0154G-E002
Process FMEA SKD 4	[redacted]01A SKD4 SAAM FMEA-0154B-E010
Process FMEA SKD 5	[redacted]01A SKD5 SAAM FMEA-0154B-E009
Process FMEA SKD 6 SAAM1 [redacted]	[redacted]SKD6 SAAM FMEA-0154B-E005 [redacted]
Process FMEA SKD 6 SAAM2	[redacted]SKD6 SAAM FMEA-0154B-E007 [redacted]
Process FMEA SKD 6 SAAM3	[redacted]SKD6 SAAM FMEA-0154B-E014 [redacted]
Process FMEA [redacted] product assembly (clinical batch)	[redacted]GP2017_40_RA-PR
[redacted] Auto-Injector Assembly Process FMEA [redacted] [redacted]	RA-140-101-15-12-001
[redacted] Auto-Injector Assembly Process FMEA Summary Repor[redacted]	RA-140-101-15-12-003
Risk Estimation & Evaluation Report [redacted]	0154-011-RM-S004

10.LABELING

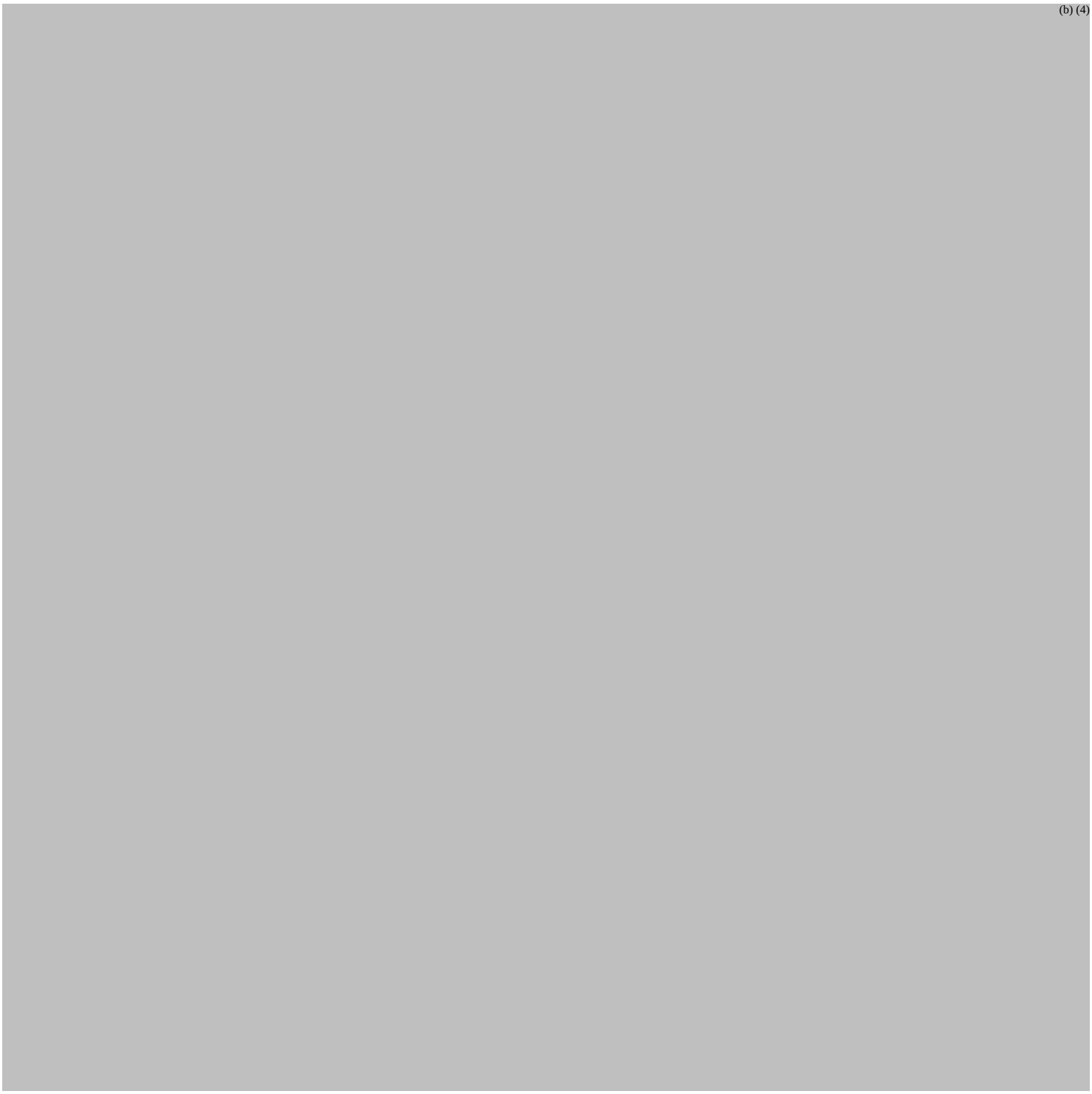
Prefilled syringe label



INSTRUCTIONS FOR USE-HYRIMOZ™ (b) (4) (adalimumab-(b) (4)) Single-dose pre-filled Syringe with BD UltraSafe Passive™ Needle Guard and add-on finger flange

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

(b) (4)



11.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

PFS release specifications provided in the Sponsor IR dated 4-17-2018:

Table 5-2 Extractable volume of GP2017_PFS_(b) (4)_40_(b) (4) during design verification and transport validation

Test	Sample size [n]	Specification	Result (mean)	Evaluation
Extractable volume: design verification	60	≥(b) (4) mL	0.8 mL	PASS
Extractable volume: after transport validation	5	≥ mL	0.8 mL	PASS

Table 5-3 GP2017_PFS_(b) (4)_40_in (b) (4) break-loose and gliding force design verification testing

Test	Description	Sample size [n]	Acceptance criteria	Result (mean) [N]	Result [N]*	Evaluation
Break-loose force	Force required to initiate plunger rod movement	20	≤(b) (4) N	5.63	6.72	PASS
Gliding force	Force required to maintain plunger rod movement	20	≤ N	4.11	5.48	PASS

APPEARS THIS WAY ON ORIGINAL

The following release specifications are included for the device constituent:
From pg. 18 of MAF(b) (4):

Table 5. Sub-assembly Release testing performed by (b) (4)

Test	Specification
Cap Removal Torque	≦(b) (4) Nm
Activation Force	(b) (4) N
Dose Accuracy	$\bar{x} - (k \cdot s) \geqq$ (b) (4) ml; one side tolerance limit factor k at 95% CI with 0.975P
Injection Depth	(b) (4) mm
Needle Cover Safety Displacement at (b) (4)	Max. displacement: ≦(b) (4) mm
Needle Cover Displacement before Activation	(b) (4) mm
Injection Time	(b) (4)

Reviewer Comment:
The release specifications/testing are adequate.

12.QUESTIONS FROM SPONSOR FOR TYPE A/B/C MEETING

None

13.INTERACTIVE REVIEW

Prefilled Syringe IRs:

Additional information and test reports are required to determine that the Prefilled Syringe (PFS) device constituent parts combination product will function as intended throughout its life cycle. Please provide the following information:

Agency Information Request #1 (sent on 4/10/2018) - ADEQUATE
Side by side detailed comparison (device parts, dimensions, materials, pictures, syringe label) of the RLD device constituent parts combination product to ANDA device constituent parts.

Sponsor Response (received on 4/17/2018)

Reviewer Comments: The Sponsor has provided adequate side by side comparison of the RLD PFS and the ANDA PFS. The detailed comparison is under the device description section of this memo.

Agency Information Request #2 (sent on 4/10/2018) - ADEQUATE
Dose accuracy test reports and results for the PFS combination product.

Sponsor Response (received on 4/17/2018)
A response to this question can be found as part of the response to question 4 PFS. Please refer to Section5.1.

Reviewer Comments: The Sponsor's response is adequate.

Agency Information Request #3 (sent on 4/10/2018) - ADEQUATE
Risk analysis of the PFS device constituent parts combination product to include identified hazards and mitigations to reduce the risks.

Sponsor Response (received on 4/17/2018)
Question 1 Autoinjector (see Section 8) stated that the submitted (b) (4)-GP2017_40 risk management and usability engineering report "…does include adequate risk analysis documentation to ensure all the hazards associated with the device have been identified, evaluated, and mitigated." Nevertheless, it was required that "…Specifically, you should assess the risk of use of the intended drugs/biological products delivered with the injector as related to the human factors characteristics of the patient population using the intended drugs/biological products."
Based on the information provided in Question 1 Autoinjector and in an effort to provide equal level of information (b) (4) Sandoz herewith submits the GP2017_PFS(b) (4)_40_(b) (4) risk management and usability engineering report (see[Attachment 1 - GP2017_PFS_(b) (4)_40_(b) (4) RMUER]), providing an overview over performed risk management activities as well as the results. In addition, the GP2017_PFS(b) (4)_40_(b) (4) usability risk assessment (see [Attachment 2 - GP2017_PFS_(b) (4)_40_(b) (4)_RA-Ap]), which evaluates the risk an end user faces when usingtheGP2017_PFS_(b) (4)_40_(b) (4)combinationproductbyfollowingtheInstructions for Use is being submitted.

Reviewer Comments: The Sponsor's response is adequate. Please see detailed report under risk analysis section of this memo.

Agency Information Request #4 (sent on 4/10/2018)- ADEQUATE
Release specifications for the PFS device constituent parts combination product should include dose accuracy and break loose/glide force.

Sponsor Response (received on 4/17/2018)
The combination product GP2017_PFS(b) (4)_40_(b) (4) consists of a pre-filled syringe which has been assembled with the (b) (4)Needle Safety Device (b) (4) (NSD).The NSD inturnconsistsoftheneedleguardassembly,-plungerrodandadd-onfinger flange. The NSD is not part of the container closure as it neither gets into contact with the

sterile content of the pre-filled syringe or the sterile fluid path, nor is it intended to provide additional protection to the container closure system.

5.1.1 Dose accuracy/Extractable volume

For GP2017_PFS_(b) (4)_40_(b) (4) the entire volume is injected by manually pushing the plunger rod down until the end of the syringe. As such, the relevant test is considered to be "extractable volume" instead of dose accuracy.

Release specifications for extractable volume have been set on the level of the GP2017 bulk PFS (drug product (DP)-filled syringe as described in Module 3.2.P). Please refer to Table 5-1 for the batch release specification for extractable volume.

Table 5-1 Extractable volume batch release specification

Test	Analytical Procedure	Specification
Extractable volume	Weighing	≥ (b) (4) mL

For the full set of GP2017 bulk PFS release and shelf life specifications, please refer to [Module 3.2.P.5.1] and for the Justification of Specifications, please refer to [Module 3.2.P.5.6].

The extractable volume of GP2017_PFS_(b) (4)_40_(b) (4) is not affected by the NSD, since the NSD gets activated only once the plunger rod has been fully pushed down, i.e. once the full content of the PFS has been expelled. This has been confirmed by performing tests for extractable volume performed on fully assembled combination products (i.e. GP2017_PFS_(b) (4)_40_(b) (4) in the course of design verification as well as transport validation. This information has been provided in [Module 3.2.R Technical summary needle safety device Table 9-2] for design verification testing and [3.2.R Technical summary needle safety device Table 9-8] for transport validation. Please find a summary in the following Table 5-2.

Table 5-2 Extractable volume of GP2017_PFS_(b) (4)_40_(b) (4) during design verification and transport validation

Test	Sample size [n]	Specification	Result (mean)	Evaluation
Extractable volume: design verification	60	≥ (b) (4) mL	0.8 mL	PASS
Extractable volume: after transport validation	5	≥ mL	0.8 mL	PASS

The testing of extractable volume in the course of the transport validation also confirms that samples going through the validated manufacturing process and additional mechanical stress testing in the course of the transport validation fulfill the specification of extractable volume.

Consequently, it is considered adequate to control the extractable volume as part of the batch release on the level of the GP2017 bulk PFS.

Reference ID: 4306205

5.1.2 Break-loose and gliding force

Break-loose and gliding force testing is not considered as needed for the fully assembled GP2017_PFS_(b) (4)40_(b) (4) combination product since the NSD gets activated only once the plunger rod has been fully pushed down, i.e. once the plunger head contacts the syringe needle guard wings. At this stage, neither break-loose, nor gliding forces play a role anymore.

Thus, it can be concluded that the NSD has no impact on break loose and gliding forces of the plunger stopper, and vice versa, neither the break-loose nor the gliding force can impact the functionality of the NSD. During the assembly process (assembly of the PFS with the NSD) neither the NSD nor the equipment get into contact with the sterile content of the syringe. Consequently, it is considered to be sufficient if break-loose and gliding force measurements are routinely performed on the level of the PFS.

However, to confirm this assessment both break-loose and gliding force tests have been conducted on the fully assembled GP2017_PFS_(b) (4)_40_(b) (4) combination product during development.

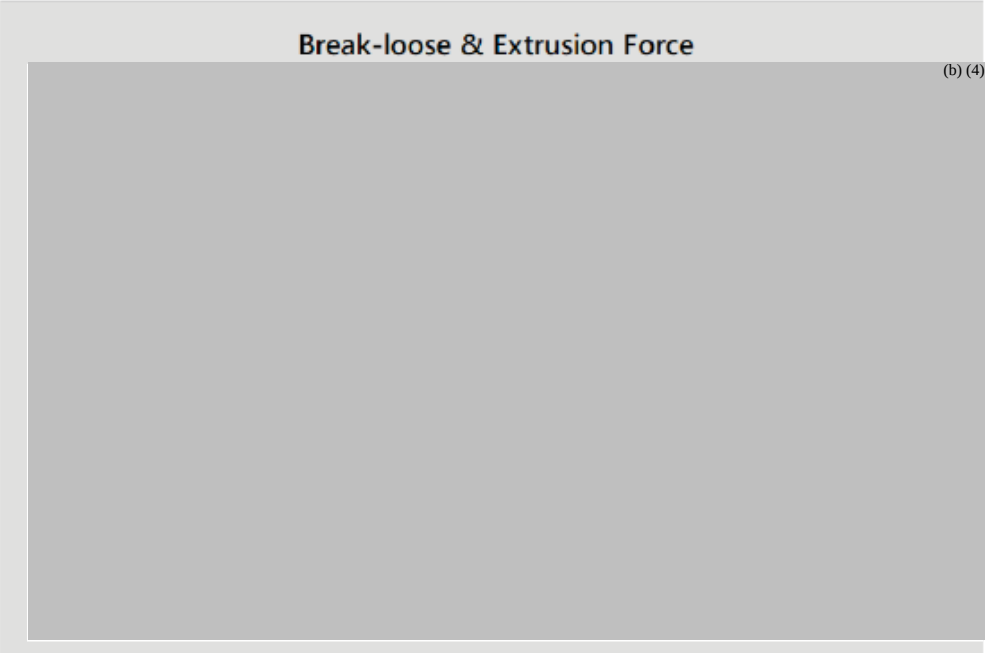
Currently no specifications exist for the break-loose and gliding force. The acceptance criteria applied during development (design verification) for the break-loose and gliding force measurements on the level of the fully assembled GP2017_PFS_(b) (4)_40_(b) (4) combination product were therefore derived from a formative human factors evaluation. In the course of this study acceptable levels of break-loose and gliding forces have been determined for patients suffering from autoimmune diseases such as rheumatoid arthritis or psoriatic arthritis (i.e. users representative for the intended user population of GP2017). The result of this study was that (b) (4) N is an acceptable limit for both break-loose and gliding force. Therefore, this limit has been used for the design verification testing on the fully assembled GP2017_PFS_(b) (4)_40_(b) (4) combination product.

Table 5-3 GP2017_PFS_(b) (4)_40_(b) (4) break-loose and gliding force design verification testing

Test	Description	Sample size [n]	Acceptance criteria	Result (mean) [N]	Result [N]*	Evaluation
Break-loose force	Force required to initiate plunger rod movement	20	≤ (b) (4) N	5.63	6.72	PASS
Gliding force	Force required to maintain plunger rod movement	20	≤ N	4.11	5.48	PASS

*The result has been calculated as (b) (4) s the k-value chosen based on the criticality of the test and applicable procedures and where "s" is the standard deviation.

Figure 5-1 Graphical representation of break-loose and gliding force test results



Note: The term extrusion force in this figure is synonymous for gliding force

As can be seen from Table 5-3 and Figure 5-1, the results for both break-loose and gliding force are far below the limit that was found to be acceptable in human factors studies with patients representative of the GP2017 user population.

In addition, break-loose and gliding forces have also been measured in the course of the transport validation.

Table 5-4 GP2017_PFS_(b) (4).40(b) (4) break-loose and gliding force during transport validation

Material	Sample size [n]	Results (mean)	
		Break-loose force [N]	Gliding force [N]
Unstressed	20	5.06	2.46
Mechanically stressed	20	4.42	2.49

The testing of break-loose and gliding forces in the course of the transport validation also confirms that samples going through the validated manufacturing process and additional mechanical stress testing in the course of the transport validation do not exhibit increased values for these two tests.

Break-loose and gliding force are considered as critical quality attributes due to the potential impact on the performance of the combination product. Therefore, these parameters will be included in the release specifications of the GP2017 bulk PFS. For break-loose and gliding forces, a method for measurement at a speed of (b) (4) mm/min was validated recently and will be used for release testing of the GP2017 bulk PFS in order to ensure a robust function with the needle safety device.

So far, only a very limited amount of development data is available for GP2017 which is not considered to be appropriate for setting meaningful specifications. Therefore, Sandoz proposes to generate additional data from commercial batches in order to define robust release and shelf life specifications.

Sandoz herewith commits to implement the specifications as soon as data from DP manufactured with five additional syringe barrel batches including end of shelf life data is available.

The update of applicable 3.2.P Modules will be submitted with the next annual report as soon as all required data are available.

Reviewer Comments: The Sponsor's response is adequate and they have provided acceptable release specifications.

Agency Information Request #5 (sent on 4/10/2018)- ADEQUATE

Packaging/shipping validation studies for the PFS device constituent parts combination product such as dose accuracy and break loose/glide force.

Sponsor Response (received on 4/17/2018)

Transport validation including analytical testing of the drug product characteristics has been performed as part of the transport validation. A detailed summary off the performed tests can be found in [Module 3.2.R Technical summary needle safety device, Section 9.2].

Results for extractable volume are provided both in the above mentioned dossier module as well as in the response to Question 4 PFS (see Section 5.1). Please note that results of break-loose and gliding force measurements after transport validation had not been included in the dossier, as no specifications have been set so far. These data can now be found in the response to Question 4 PFS (see Section 5.1).

Reviewer Comments: The Sponsor's response is adequate and they have provided acceptable test reports and results.

Agency Information Request #6 (sent on 4/10/2018)- ADEQUATE

Aging studies of the PFS device constituent parts combination product.

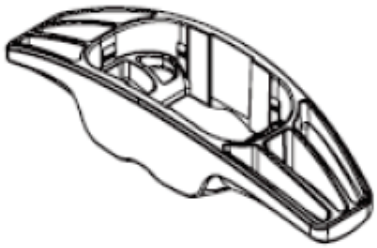
Sponsor Response (received on 4/17/2018)

The (b) (4) Needle Safety Device (b) (4) (NSD) consists of the needle guard assembly, plunger rod and add-on finger flange. They form together the single-use device constituent parts of the combination product GP2017_PFS_(b) (4)_40_(b) (4) (see Figure 7-1).

Figure 7-1 [redacted] **Needle Safety Device** [redacted] **Components**

Needle Guard

Plunger rod



Add-on finger flange

These components have a shelf life of [redacted] years, which is based on aging studies conducted by the manufacturer [redacted]

Table 7-1 [redacted] **Documents confirming shelf life**

Document title	Document code
[redacted]	

The following data created by [redacted] currently exists and confirms the shelf life of the device components:

1. Accelerated aging equivalent to [redacted] years real time using Arrhenius equation with Q[redacted]
2. 4 years real time aging at 20.5 ± 2°C
3. 3 years refrigeration aging at 5 ± 3°C (simulating refrigerated storage of finally assembled products including a temperature sensitive drug product such as GP2017)

All data created confirm that the device components are stable for [redacted] years without any impact on functionality. In the following, summaries from these studies are presented:

Table 7-2 **Accelerated aging equivalent to [redacted] years real time [redacted]**

Test	Description	Acceptance criteria	T0	[redacted] years equivalent accelerated aging
Guard color	Color matches the defined	Correct color	PASS	PASS

		X100L		
match	(b) (4) color	(b) (4)		
Activation cycle force	Spring reaction force during activation all the way through the lockout		PASS	PASS
Compression force	Force required to override the activated locked guard to the un-activated position		PASS	PASS
Separation force	Force required to separate the guard from the body when the assembled device has been activated in its locked position		PASS	PASS
Syringe spin test	Syringe spins freely at least in one direction	Syringe spins freely at least in one direction	PASS	PASS
Triggering test	Confirmation that the needle guard triggers correctly and locks in the activated state	Correct triggering along with full activation into locked position	PASS	PASS
Plunger rod color match	Color matches the defined (b) (4) color	Correct color (b) (4)	PASS	PASS

Table 7-3 4 years real time aging at 20.5 ± 2°C

Test	Description	Acceptance criteria	T0	1 year real time aging	2 years real time aging	3 years real time aging	4 years real time aging
Activation cycle force	Spring reaction force during activation all the way through the lockout	(b) (4)	PASS	PASS	PASS	PASS	PASS
Compression force	Force required to override the activated locked guard to the un-activated position		PASS	PASS	PASS	PASS	PASS
Separation force	Force required to separate the guard from the body when the assembled device has been activated in its locked position		PASS	PASS	PASS	PASS	PASS
Syringe spin test	Syringe spins freely at least in one direction	Syringe spins freely at least in one direction	PASS	PASS	PASS	PASS	PASS
Triggering test	Confirmation that the needle guard triggers correctly and locks in the activated state	Correct triggering along with full activation into locked position	PASS	PASS	PASS	PASS	PASS

Table 7-4 3 years refrigeration aging at 5 ± 3°C

Test	Description	Acceptance criteria	T0	6 months	12 months	18 months	24 months	30 months	36 months
Activation cycle force	Spring reaction force during activation all the way through the lockout	(b) (4)	PASS	PASS	PASS	PASS	PASS	PASS	PASS
Compression force	Force required to override the activated locked guard to the un-activated position		PASS	PASS	PASS	PASS	PASS	PASS	PASS

Reviewer Comments: The Sponsor's response is adequate and they have provided acceptable test reports and results.

Autoinjector IRs:

Agency Information Request #7 (sent on 4/10/2018)- ADEQUATE

In your device risk management document, (b) (4)-GP2017_40_RMUER_02 ("Risk Management and Usability Engineering Report") you state the following with regards to the risk analysis: *"Hazard identification, risk estimation and evaluation for the device constituent part of the combination product have been carried out by* (b) (4) *according to their internal procedures, in collaboration with and with the final approval of Sandoz. Hazard Identification Checklist,* (b) (4) *Design-FMEA and* (b) (4) *Process FMEAs have been used as input to the risk estimation & evaluation report."* The information provided in this document does include adequate risk analysis documentation to ensure all the hazards associated with the device have been identified, evaluated, and mitigated. The FDA Guidance Document, *"Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products,"* (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf) recommends that you conduct a risk analysis that considers the overall product and includes both the injector and drug/biological product for injection. Specifically, you should assess the risk of use of the intended drugs/biological products delivered with the injector as related to the human factors characteristics of the patient population using the intended drugs/biological products. It is not

clear if the risk analysis performed by (b) (4) and approved by Sandoz incorporates recommendations for the risk analysis per FDA Guidance. Multiple documents are referenced in Table 3-2 of Document (b) (4)-GP2017_40_RMUER_02 that may include this information, but were not included in the BLA submission. If the documents referenced in Table 3-2 incorporate the above recommendations, provide these documents. If these recommendations have not been addressed, provide updated risk analysis documentation that includes the full identification, evaluation and mitigation of all hazards associated with the device, and provide any additional verification documentation as necessary.

Sponsor Response (received on 4/17/2018)
The appropriate assessment that evaluates the risks users face when using the (b) (4)- GP2017_40 according to the Instruction for Use is provided in Table 3-2 of Document (b) (4)-GP2017_40_RMUER_02 as "Application/Usability Risk Assessment; (b) (4)-GP2017_40 RA-Ap". This document is now provided as [Attachment3– (b) (4)-GP2017_40_RA-Ap].
A complete summary of human factors engineering activities has been already provided in the BLA (please refer to [Module 3.2.R Technical summary (b) (4) device–attachment2]).

Reviewer Comments
The updated risk analysis documentation is acceptable.

The sponsor also provided updated user requirement specification documents and traceability matrices that completes the design control aspect of the risk documentation.

Agency Information Request #8 (sent on 4/10/2018)- ADEQUATE
You state the following in 3.2.R Technical Summary (b) (4) Device (722-1263-32r-tech-sum-(b) (4)-dev-790-2-0) with regards to device shelf life of the autoinjector device: "Shelf life was determined by (b) (4) using accelerated aging studies. The aged samples were inspected and tested via visual inspection and functional tests, and met the performance requirements. Detailed information on the aging tests performed is presented in the MAF-(b) (4)." This testing provided in MAF (b) (4) referenced was deficient and did not adequately demonstrate the device meets a shelf life of (b) (4) years. An information request will be sent to the MAF holder, (b) (4) to resolve this deficiency.

Sponsor Response (received on 4/17/2018)
Sandoz acknowledges that a deficiency letter will be sent directly to the MAF holder (b) (4) and has also informed the MAF holder to expect it.
However, to avoid any potential misunderstandings, Sandoz would like to clarify that"…the device meets a shelf life of (b) (4) years" is not correctly representing the claim made in the submitted BLA. -[Module3.2.R Technical summary (b) (4) device, Section4.8.2] states:
"The shelf life of GP2017-(b) (4) auto injector subassemblies prior to final assembly is (b) (4) years and after final assembly it is (b) (4) years, thus providing for a maximum shelf life of (b) (4) years.
Shelf life was determined by (b) (4) using accelerated aging studies. The aged samples were inspected and tested via visual inspection and functional tests, and met the performance requirements. Detailed information on the aging tests performed is presented in the MAF-(b) (4)."

Once these two sub-assemblies have been assembled with a syringe, the shelf life of the assembled product is maximally (b) (4) years. However, the actual shelf life of the final assembled product is depending on the shelf life of

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the drug product filled in the syringe. For GP2017, the shelf life of the GP2017 bulk pre-filled syringe as -claimed in the submitted BLA is 24months when stored at intended storage conditions. For the shelf life of the finally assembled combination product (b) (4)-GP2017_40, [Module 3.2.R Technical summary (b) (4) device, -section4.8.3]states: "The defined shelf life of the final, assembled (b) (4)-GP2017_40 is based on the shelf life of the drug product constituent part as described in [Module 3.2.P.8.1]. The combination product has to be stored at36°F to 46°F (2°C to 8°C)."

Therefore, a shelf life of (b) (4) years for the device as stated in the question reflects the combined shelf life of the device components before final assembly ((b) (4) years)and the shelf life of the assembled device after final assembly (b) (4) years). However, as stated in the submitted BLA and explained above, the actual shelf life of the marketed combination product (b) (4)-GP2017_40 is based on the shelf life of the drug product constituent part, which is 24 months.

Reviewer Comments
This issue is discussed further under the Information Requests for MAF Holder (b) (4)

Agency Information Request #9 (sent on 4/10/2018)- ADEQUATE
The documents, "0154-011-VE-T002" (Design Verification Master Report) and "0154-011-VE-T002," (Design verification protocol for Assessment by project team for GP2017-(b) (4)-40) are referenced Section 8 of document (b) (4) GP2017_40_DVERSR_02 (Design Verification Summary Report) submitted under module 3.2.R of BLA 761071. These documents are also referenced in MAF (b) (4) as testing performed by Sandoz to verify the Design Input Requirements 4.11, 4.12, 4.13, 4.14, 4.19, 4.22, 4.27, 4.29, 4.30, 4.31, 4.32, 4.33, 4.34, 4.35, 4.36, 4.38, 4.39, and 10.2 have been met. These complete documents were not included in the BLA, nor was it provided in the Master File. Provide these aforementioned test protocols and reports to ensure the (b) (4)-GP2017_40 meets its design input requirements and is safe and effective for use.

Sponsor Response (received on 4/17/2018)
The requested documents are provided as attachments [Attachment4 -0154-011-VE-T002] and [Attachment5–0154-011-VE-S002] to this response document.

Reviewer Comments
The sponsor provided this information, and it is reviewed in Section 4.2 of this memo.
The information was determined to be adequate.

Agency Information Request #10 (sent on 4/10/2018)- ADEQUATE
You have referenced a multitude of SNZ documents in Design Verification Summary Report ((b) (4) GP2017_40_DVERSR_02) that are not included in the submission. The user requirements specifications ((b) (4) GP2017_40_URS), (b) (4)-GP2017_40 Product Description ((b) (4)-GP2017_40_PRDESC), Traceability Matrix for (b) (4) GP2017_40 ((b) (4)-GP2017_40_TRAMA) are referenced to include critical design control information yet cannot be found in the eCTD. Provide these documents.

Sponsor Response (received on 4/17/2018)
The requested documents are provided as attachments to this response document. Please refer to [Attachment 6-(b) (4)-GP2017_40_URS], [Attachment 7–(b) (4)-GP2017_40_URS_(b) (4)],

[Attachment 8 - (b) (4) -GP2017_40_PRDESC] and [Attachment 9 - (b) (4) GP2017_40_TRAMA]

Reviewer Comments
The sponsor provided this information, and it is reviewed in Section 4.2 of this memo.
The information was determined to be adequate.

MAF Holder IR:

Agency Information Request #11 (sent on 4/10/2018) - ADEQUATE
You have included in Attachment 4 of MAF (b) (4) an accelerated aging test protocol and report for the (b) (4) autoinjector platforms as substitution for the GP2017-(b) (4) autoinjector system. While this testing appropriately demonstrates the functionality of the device components that are identical between the (b) (4) device and the GP2017-(b) (4) device, it does not demonstrate functionality where they differ, most notably dose accuracy and injection time. While the test protocols described in 0154-004-ATR-T001 for dose accuracy and injection time are acceptable, they are not applicable to the GP2017-(b) (4) as the device delivers 0.8mL of fluid and does not have an identical plunger rod. Please repeat the aging verification testing described in 0154-004-ATR-T001 for dose accuracy and injection time using the final finished GP2017-(b) (4) device.

MAF Holder Response (received on4/17/2018)

(b) (4)

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(b) (4)

[redacted]

In addition to the design verification I aging program performed by (b) (4) Sandoz has performed stability testing using the marketable GP201 7-(b) (4) device combination product including GP2017 filled syringes. This stability testing has been perfo1med on batches assembled in the comse of the assembly-and packaging process validation at (b) (4) and includes dose accuracy and injection time testing.

To facilitate the review by the agency, available Sandoz stability results are provided below in Tables 2-1 and 2-2 to support (b) (4) response. All results fulfilled the acceptance criteria.

Table 2-1 Functional testing results for (b) (4) GP2017_40 at intended storage condition (testing performed by Sandoz)

Testing attribute	Batch #016C16A					Batch #017C16A					Batch #018C16A				
	Pull points [months]					Pull points [months]					Pull points [months]				
	0	6	9	12	18	0	6	9	12	18	0	6	9	12	18
Dose accuracy (b) (4)	0.782	0.783	0.794	0.798	0.792	0.793	0.795	0.800	0.798	0.789	0.799	0.800	0.804	0.804	0.797
Injection time (b) (4)	7	6	6	6	5	6	6	6	6	5	8	6	6	7	5

Table 2-2 Functional testing of (b) (4) GP2017_40 at the accelerated storage condition (testing performed by Sandoz)

Testing attribute	Batch #016C16A		Batch #017C16A		Batch #018C16A	
	Pull points [months]					
	0	6	0	6	0	6
Dose accuracy (b) (4)	d.i.c.	0.797	d.i.c.	0.796	d.i.c.	0.803
Injection time (b) (4)	d.i.c.	7	d.i.c.	7	d.i.c.	7

*. d.i.c.: done with intended condition, please refer to Table 2-1.

Reviewer Comments

Based on the near identical nature of the spring component and rear assembly of the (b) (4) and (b) (4) GP2017-40 devices, the rationale presented here for age-dependent degradation of function is acceptable. Additionally, no notable differences were found in the devices during the rigorous design verification testing and comparison of the (b) (4) and GP2017-40 devices.

Sandoz provided dose accuracy and injection time testing at 18 months, 6 months short of the intended shelf life of 24 month. This information, in combination with the age-degradation rationale, are acceptable to demonstrate the shelf life of the device.

The response adequately addresses the agency's concerns.

14.OUTSTANDING DEFICIENCIES

None

15.RECOMMENDATION

Device Constituents Parts of the Combination Product are Approvable

15.1. Recommended Post-market commitments/post-market requirements-None

16.APPENDIX

Reference ID: 4306205

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

GENERAL HOSPITAL DEVICES BRANCH
CONSULT MEMORANDUM

Date: July 2, 2018

To: Kathleen Fitzgerald
CDRH/ODE/DAGRID/GHDB

From: Pete Basile
CDRH/ODE/DAGRID/GHDB

Subject: Consult for BLA 761071, Sandoz Biopharmaceuticals, GP2017

Applicant	Sandoz Biopharmaceuticals
Indication for Use	Adalimumab is a TNFα inhibitor used for the treatment of various autoimmune diseases. The present marketing authorization application seeks licensure for indications for which the US licensed reference product Humira® is approved (with the exception of indications covered by orphan drug exclusivity)
Drug / Biologic Constituent	GP2017 (INN: adalimumab) 40mg/0.8mL
Device Constituent	(b) (4) Autoinjector ((b) (4)-GP2017_40)

Recommendation: Autoinjector component of combination product approvable for use with GP2017.

Digital Signature Concurrence Table	
Reviewer	
Branch Chief	

TABLE OF CONTENTS

1. PURPOSE/BACKGROUND

1.1. Scope

The lead reviewer, Kathleen Fitzgerald, requested the following engineering review:

"This is a combination product that consists of a single use PFS and autoinjector. This is a re-submission to a CR. The new submission starts at sequence 0005 date 10-30-2017. Please review the autoinjector functional performance test reports. LOAs are present to review the device information in the MAF. Autoinjector information is located under sequence 0005 3.2.R tech summary (b) (4) device, attachments 2-4 and IMAGE 2000 under MAF (b) (4)."

This review will cover all functional performance aspects of the autoinjector device. The PFS syringe device is not covered under the scope of this review. Human factors, labeling, biocompatibility and sterility of the autoinjector will not be covered under the scope of this review.

1.2. Prior Interactions

None.

1.3. Indications for Use

Reference ID: 4306205

Product (Drug)	Indications for Use
GP2017 (INN: adalimumab) 40mg/0.8mL	Based on the concept of extrapolation of indications, licensure of GP2017 is sought for all indications as approved for Humira®

Product (Device)	Indications for Use
(b) (4) Autoinjector ((b) (4)-GP2017_40)	(b) (4)

2. ADMINISTRATIVE

2.1. Documents Reviewed

Document Title	Document Number	Date - Version	Location
Technical Summary (b) (4) Device	722-1263-32r-tech-sum-(b) (4)-dev-790-2-0	11-Aug-2017	eCTD Module 3.2.R
MAF (b) (4)	MAF (b) (4)	04-Apr-2016	Image2000
Technical Summary (b) (4) Device – Attachment 3	(b) (4) GP2017_40_RMUER_02	05-Sept-2016	eCTD Module 3.2.R
Design Verification Summary Report	(b) (4) GP2017_40_DVERSR_02	28-Aug-2018	eCTD Module 3.2.R
Attachment 3– (b) (4) GP2017_40_RA-Ap	(b) (4)-GP2017_40_RA-AP1_04	30-Jan-2018	eCTD Module 3.2.R
Attachment 4 -0154-011-VE-T002	N/A	N/A	eCTD Module 3.2.R
Attachment 5– 0154-011-VE-S002	N/A	N/A	eCTD Module 3.2.R
User Requirement Specification	(b) (4)-GP2017_40_URS	N/A	eCTD Module 3.2.R
Attachment 7	(b) (4) GP2017_40_URS_(b) (4)	16-Apr-2018	eCTD Module 3.2.R
Product Description, Intended Use, Indication, Classification (Attachment 8)	(b) (4)-GP2017_40_PRDESC	16-Apr-2018	eCTD Module 3.2.R
Traceability Matrix (Attachment 9)	(b) (4) GP2017_40_TRAMA	16-Apr-2018	eCTD Module 3.2.R
MAF (b) (4)/A001	Cover Letter	02-May-2018	Image2000

3. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

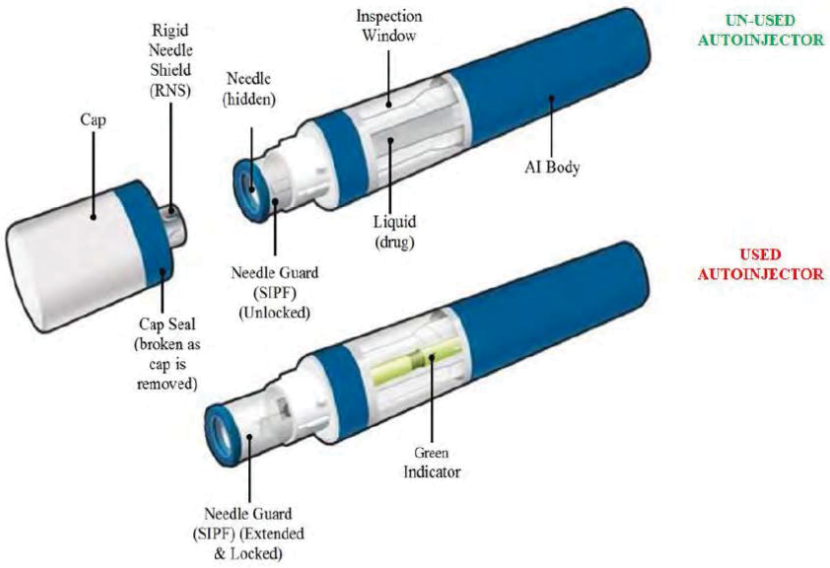
The (b) (4)-GP2017_40 is a single use drug-device combination product consisting of an administration device and a drug product constituent part. The device constituent part is a single-use autoinjector ((b) (4) AI), and the drug component is a 40 mg / 0.8 mL solution of GP2017 provided in a prefilled syringe with a staked needle. The prefilled syringe is assembled into the autoinjector and forms a single unit with the autoinjector which is not to be separated.

The (b) (4)-GP2017_40 is a fixed dose, single dose needle-based injection system with automated functions according to ISO 11608-1 and ISO 11608-5. The sole function of the (b) (4) AI is to deliver a single, fixed dose, subcutaneous injection of GP2017.

The (b) (4) AI is composed of a main outer body and a prefilled syringe (PFS) carrier assembly inside; the device is spring powered and is designed to administer the entire contents of the PFS in one dose. The (b) (4) AI is not part of the sterile fluid path and does not have any contact with the drug or biologic contained within the prefilled syringe.

(b) (4)

Figure 4-4 Graphical depiction of the (b) (4)-GP2017_40 and its key components



The (b) (4)-GP2017_40 consists of the following parts (as shown in Figure 4-4)

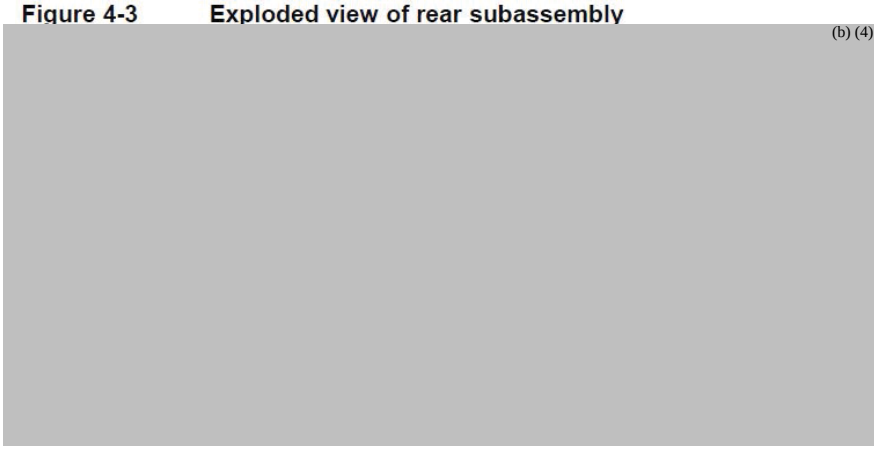
- Cap (protects the needle before use)
- Cap Seal (tamper evidence feature)
- Rigid Needle Shield (RNS) (seals the syringe and protects the needle before use) – part of the PFS
- Needle (inserts into the skin)
- Needle Cover (Sharps Injury Prevention Feature (SIPF))

- AI Body (contains the injector mechanism)
- Inspection Window (allows user to check the progress of the injection (green indicator) and check the appearance of the drug before use)
- Green Indicator (shows the progress of the injection as it progresses through the inspection window during injection)

Figure 4-1 Composition of (b) (4)-GP2017_40 (exploded view)

Figure 4-2 Exploded view of front subassembly

Figure 4-3 Exploded view of rear subassembly



The injection process starts with the removal of the cap. By twisting off the cap, the rigid needle shield of the syringe is removed. Once the cap is removed, the needle remains covered and completely hidden by the needle cover.

The AI is a push-click device: When the autoinjector is pressed gently against the skin, the extended Needle Cover is pushed back into the front subassembly and the device will activate. By actuating the process, the needle is inserted automatically into the patient's skin, and following the needle insertion the injection process starts automatically. The start of the injection process is indicated by a first click. During the injection, the plunger rod drives the rubber stopper, emptying the content of the syringe. The injection process can be monitored through the inspection window on the autoinjector by observing the movement of the green plunger rod. A second click announces that the injection is almost finished. The injector is kept in place at the injection site until the green plunger rod has stopped moving.

When the device is removed from the injection site, the needle cover automatically extends to completely cover the needle and irreversibly locks in the extended position to prevent inadvertent needle stick injuries. It is not possible to re-attach the cap.

The needle-based injection mechanism is spring powered and designed to administer the entire content of the prefilled syringe in one dose. The entire content of the prefilled syringe is delivered to the patient at the fixed rate. The dosage is defined by the fill volume of the prefilled syringe.

<u>Comparison to previously approved device:</u>
The autoinjector of (b) (4)-GP2017_40 is based on the same technology as the SureClick®/ (b) (4) autoinjector. (b) (4)

The mechanical principles of construction of the (b) (4)-GP2017_40 are based on the proven technology of the (b) (4) autoinjector. Compared to the latter, a technical simplification was made for the (b) (4)-GP2017_40 autoinjector, in order to improve the ease of use for patients with limited joint mobility or dexterity. While the (b) (4) autoinjector is actuated via a button, the (b) (4)-GP2017_40 is actuated by pushing the needle cover against the injection site.

The GP2017-(b) (4) Autoinjector has the following dimensions and specifications:

Device Characteristic	Description / Specification
Injector Name	GP2017-(b) (4) Autoinjector
Cap Removal Torque	≦ (b) (4) Nm
Activation Force	(b) (4) N
Injection Time	≦ (b) (4) sec
Injection Depth	(b) (4) mm

Needle Cover Override Force	Min: (b) (4) N Max: (b) (4) displacement of the needle cover
Separation Force between Cap and Front End Cover	(b) (4)
Needle Cover Displacement before Activation	(b) (4) mm
Dose Accuracy	$\bar{x}$ - (k*s) ≧ (b) (4) ml; one sided tolerance limit factor k at 95% CI with 0.975P
Length	(b) (4) mm

4. ENGINEERING REVIEW

4.1. Design Control Summary

4.1.1. Design 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	X		Attachment 6 - (b) (4)-GP2017_40_URS; Attachment¬ 7¬–¬ (b) (4)-GP2017_40_URS_ (b) (4)
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		Attachment4 -0154-011-VE-T002, (b) (4) GP2017_40_DVERSR_02; Attachment 5 - 0154-011-VE-S002
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		Attachment 3 - (b) (4)-GP2017_40_RA-Ap; (b) (4) GP2017_40_RMUER_02
Validation Data • Human factors • Clinical data	X		(b) (4)-GP2017_40_RMUER_02
Traceability Documentation	X		Attachment 9 - (b) (4)-GP2017_40_TRAMA

***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.**

4.1.2. Design Control Review

The design control can be summarized via a representative screenshot of the traceability matrix ((b) (4) GP2017_40_TRAMA):

Zoomed in on trace between design input and verification testing: (pg.2)

4.1.3. Risk Analysis

Reviewer Comment:
The sponsor provided updated risk analysis documentation in response to Information Request 1. See Section 4.3 of this memo.

Reference ID: 4306205

4.2. DESIGN VERIFICATION AND VALIDATION REVIEW

4.2.1. Summary of Design V&V Attributes

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

Reviewer Comment:
User Requirements and Traceability documentation are review in Section 4.1.2, under the design control review.

4.2.2. Design Verification

A significant portion of the design verification testing was not completed on the final, finished design of the device. MAF (b) (4) states the following with regards to the different device designs:

"For clarification, (b) (4) would like to point out that these three injectors, (b) (4) (0154-002), (b) (4) (154-004) and GP2015-(b) (4) 50-(0154-010), utilizes the same device design, the only difference is the pharmaceutical drug/syringe content. The GP2017-(b) (4)-40 Autoinjector utilizes the same common components as the other (b) (4) devices [(b) (4) (0154-002), (b) (4) (154-004) and GP2015-(b) (4) 50-(0154-010)], except for three components.

The three different components are the Rear end cover, Plunger rod and Plunger spring. The differences are 1) (b) (4) and 2) (b) (4). The function of the revised spring, Plunger rod and Rear end cover are identical to the same components used in other (b) (4) devices."

The components of the multiple (b) (4) devices are compared in the table below:

Product name	[redacted]	[redacted]	GP2015[redacted]-50	GP2017[redacted]40
Project code	0154-002	0154-004	0154-010	0154-011
Needle cover extension	Same	Same	Same	Same
Actuator Sleeve				
Syringe Driver				
Needle Cover				
Syringe Carrier				
Front End Cover				
Syringe Collar				
Actuator				
Front Shell				
Cap[redacted]				
Spring Guide Rod				
Needle Cover Spring				
Shield Remover				
Rear End Cover				Different
Plunger Rod				Different
Plunger Spring				Different

Table 9-1 Performance requirements of [redacted]GP2017_40

Design Input	Performance Requirement	Test Item	Test Method	Acceptance Criteria	Results
DIR 4.1	The injection time into air shall be less than or equal to (≤) [redacted] seconds.	Injection time	Measure the time required for a device to expel the drug contents completely from the starting point to the completion point of the injection. This is measured by a detailed video camera recording system	[redacted]	PASS
DIR 4.2	The delivered volume shall be equal or larger than (≥) [redacted] mL calculated according to the dose accuracy requirement specified in ISO 11608-1 (D1, N=60, one side tolerance limit factor k at 95% CI with 0.975P)	Dose accuracy	Weight the mass expelled from the PFS to ensure that the drug was expelled completely during injection. Gram is converted into ml and a micro-balance scale is used for measurement. Record the value. The method is aligned with ISO 11608-1:2012.		PASS
DIR 4.3	The needle injection depth shall be [redacted] mm	Injection depth	Measure the Needle length exposed during injection through a detailed video camera recording system. Record the distance value.		PASS
DIR 4.4	The displacement of the Needle cover before activation shall be between [redacted] mm [redacted] mm (excluding initial play)	Needle cover displacement at activation	When the activation force is measured, the Needle cover displacement length is also measured in the tensile testing system		PASS
DIR 4.5	The activation shall occur at a minimum distance of [redacted] mm between the Needle cover extension and the Front end cover	Activation point inspection	Hold the autoinjector vertically by hand with a standard distance gauge placed perpendicularly against the length of the Needle cover. Replace the gauge with shorter gauges until activation. When activated, record the value of the gauge between the Needle cover extension and the Front end cover		PASS
DIR 4.6	The needle point shall be at least [redacted] mm inside the edge of the needle cover after completed injection, when the Needle cover is exposed to a force of, at least, [redacted] N	Needle cover distance	Expose the Needle cover to [redacted] N followed by measurement of the distance between the Needle tip and the outer edge of the Needle cover extension with a digital meter indicator. According to ISO 11608-5:2012		PASS
DIR 4.7	The force on the Needle cover to trigger activation shall be between [redacted] and [redacted]	Activation force	Measure the force applied on the Needle cover to trigger activation through a tensile testing system. Record the force value.		PASS

Design Input	Performance Requirement	Test Item	Test Method	Acceptance Criteria	Results
DIR 4.8	The Needle cover override force after injection shall be at least (b) (4)N (instantaneous) with less or equal to (≤) (b) (4)mm displacement of the Needle cover	Needle cover safety, displacement at (b) (4)N	Verify by length that a force of ≥ (b) (4)N cannot push the Needle cover back into the Front subassembly after injection, and that the needle cannot be seen after the Needle cover withstood (b) (4)N. Test performed with fixture and tensile testing system.	(b) (4)	PASS
DIR 4.9	The separation force between Front shell and Rear end cover shall be at least (b) (4)N	Rear end cover and Front shell separation force	Assemble the Rear end cover and Front shell. Activate the load-cell on the tensile testing system and separate the Rear end cover and the Front shell. Record the maximum force value when they are separated.		PASS
DIR 4.10	The separation force between the Front shell and Front end cover shall be at least (b) (4)N	Front end cover and front shell separation force	Assemble the Front end cover and the Front shell. Activate the load-cell on the tensile testing system and separate the Front end cover and the Front shell. Record the maximum force value when they are separated.		PASS
DIR 4.16	The separation force between the Cap and the RNS remover shall be (b) (4)N	Cap and RNS remover separation force	Assemble the Cap and Shield remover. Activate the load-cell on the tensile testing system and separate the Shield remover from the Cap. Record the maximum force value when they are separated.		PASS
DIR 4.17	The separation force between the RNS remover and the RNS shall be (b) (4)N	Shield remover and RNS separation force	Assemble the Shield remover and a RNS (rigid needle shield) of the syringe. Activate the load-cell on the tensile testing system and push out the RNS from the Shield remover. Record maximum force value when they are separated.		PASS
DIR 4.20	The rotation torque should be ≤ (b) (4)Nm when twisting off the Cap from device with label	Cap removal torque	The torque fixture is attached on the digital torque meter and the final assembled device with label is attached onto the fixture. Then the peak torque needed to separate Cap and Shield remover from the device is recorded.		PASS
DIR 4.21	The separation force between the Cap and the Front end cover (plastic parts only) shall be (b) (4)	Cap pull off force from front end cover	Assemble the Cap, the Front end cover and the Front shell. Activate the load-cell to separate the Cap from Front end cover axially. Record the maximum force value when they are separated. (Plastic parts only).		PASS

Design Input	Performance Requirement	Test Item	Test Method	Acceptance Criteria	Results
DIR 4.25	The overall weight of the device, including filled 1 ml syringe, must not exceed (b) (4)	Total weight	After assembling the Syringe into the autoinjector, weigh the assembled device on the microbalance scale and record the value.	(b) (4)	PASS
DIR 4.26	Total length: (b) (4)mm Cap length: (b) (4)mm Max diameter (b) (4)mm	Injector measurement	Dimension measurement of autoinjector outer dimensions with 2D vision measurement machine.		PASS
DIR 4.11	The device shall give an audible feedback at the start of the injection stroke	Attribute Test	Remove the Cap manually from the autoinjector. Hold the device vertically against the injection pad and lower it (i.e. depress the Needle cover) manually until activation. After the activation when the autoinjector left the pad, control that the Needle cover can't be pushed back into the autoinjector manually.		PASS
DIR 4.12	The device shall give an audible feedback signaling "end of injection" as late in the injection stroke as practically possible	Attribute Test			PASS
DIR 4.13	The device shall have a visible end of injection indicator	Attribute Test	During injection, items as described in column 'acceptance criteria' are checked.'		PASS
DIR 4.14	It shall be possible to monitor the Plunger rod movement during the injection stroke	Attribute Test			PASS

The following functional/performance requirements can be found in MAF (b) (4):

2.1 Functional/Performance Requirements (Ambient Conditions: 18°- 28℃, 25%-75% RH)

DIR Item No.	Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
4.1	The injection time in air shall be less than or equal to (≤) (b) (4) seconds.	4.1	Yes	N/A
4.2	The delivered volume shall be equal or larger than (≥ (b) (4) ml calculated according to the dose accuracy requirements specified in ISO11608-1 ((D1, N=60, one side tolerance limit factor k at 95% CI with 0.975 P).	4.2	Yes	

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The needle injection depth shall b (b) (4) nm.	4.3	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The displacement of the Needle Cover before activation shall be between (b) (4) mm (excluding initial play).	4.4	No	
The activation shall occur at a minimum distance of (b) (4) mm between the Needle cover extension and the Front end cover.	4.5	No	
The needle point shall be at least (b) (4) mm inside the edge of the needle cover after completed injection, when the Needle Cover is exposed to a force of, at least, (b) (4) N.	4.6	No	
The force on the Needle cover to trigger activation shall be between (b) (4) (b) (4)	4.7	No	
The Needle Cover override force after injection shall be at least (b) (4) N (instantaneous) with less or equal to (≤) (b) (4) mm displacement of the Needle Cover.	4.8	No	
The separation force between Front Shell and Rear end Cover shall be at least (b) (4) N (Typical value (b) (4) N).	4.9	No	
The separation force between Front Shell and Front end Cover shall be at least (b) (4) N.	4.10	No	
The device shall give an audible feedback at the start of the injection stroke.	4.11	Yes	See Note 1
The device shall give an audible feedback signalling "end of injection" as late in the injection stroke as practically possible.	4.12	Yes	
The device shall have a visible end of injection indicator.	4.13	Yes	
It shall be possible to monitor the Plunger Rod movement during the injection stroke.	4.14	Yes	

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The device shall allow for visual inspection of the drug product, i.e. the formulation and the pre-filled syringe.	4.15	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The separation force between the Cap and the RNS Remover shall be ≥ (b) (4)N.	4.16	No	
The separation force between the RNS Remover and the RNS shall be ≥ (b) (4)N.	4.17	No	Identical device components and syringe components are used
When the Cap is twisted off from the device, any potential rotation of the RNS may not cause coring (cut out of rubber particles).	4.18	No	
The needle must be hidden before use.	4.19	Yes	See Note 1
The rotation torque should be ≤ (b) (4)Nm when twisting off the Cap from device with label.	4.20	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The separation force between the Cap and the Front end cover (plastic parts only) shall be (b) (4) (b) (4)	4.21	No	
The noise level and tactile response during activation and injection shall be acceptable by the customer.	4.22	Yes	See Note 1
The syringe needle shield must not be moved outwards from the syringe during handling/assembly in a way that the needle is exposed to microbiological contamination.	4.23	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The assembly of the PFS must be facilitated by sufficient guiding and chamfers in Front sub-assembly.	4.24	No	
The overall weight of the device, including filled 1 ml syringe, must not exceed (b) (4)	4.25	Yes	N/A

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The device shall be free from visual and functional defects after vibration testing according to ISO 11608-1:2012.	4.37	No	This property is not influenced by the difference of the 3 components and pre-filled syringe
Front subassembly: Cap (b) (4) (b) (4) Needle cover extension (b) (4) Front end cover (b) (4) (b) (4) Rear subassembly: Plunger rod Rear end cover (b) (4)	4.38	Yes	See Note 1
The cap must be designed to prevent accidental activation when removed and the user must not be able to activate the device without removing the cap.	4.39	Yes	

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
Total length: (b) (4) mm. Cap length: (b) (4) mm Max diameter (b) (4) mm	4.26	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content
The device must automatically insert the needle and inject the medication.	4.27	Yes	See Note 1
The design of the device shall be adopted for delivery of one dose with Pre filled syringe fill volume lower than (b) (4) ml.	4.28	No	
The device must comprise no more than two sub-assemblies that are to be assembled with the pre-filled syringe in a final assembly step.	4.29	Yes	
The device must have a triangular cross section, as described in the Industrial design report.	4.30	Yes	
The outer shape of the device must not have any sharp edges.	4.31	Yes	
The body of the device must have a straight shape, without curves.	4.32	Yes	
The device must be actuated by pressing the needle cover against the injection site only, without additional trigger button.	4.33	Yes	
The device must have a protective Cap, to be removed prior to injection.	4.34	Yes	
The Cap must be possible to remove by a rotational movement, using a cam curve as described in Industrial design report.	4.35	Yes	
The device must have a needle cover that locks in its outer position, protecting the needle, after injection.	4.36	Yes	

2.2 Transport and Storage/Environmental Requirements

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The transport method of (b) (4) subassemblies shall comply with ASTM 4169-09.	7.1	Yes	N/A
The device shall be free from visual and functional defects after (b) (4) mm free fall testing according to ISO 11608-1:2012.	7.2	Yes	
Injection shall be completed after sub-assemblies have been preconditioned for ≤96 hours at +55±2℃ (50±10%RH).	7.3	Yes	
Injection shall be completed after sub-assemblies have been preconditioned for ≤96 hours at -40±3℃.	7.4	Yes	
The sub-assemblies shall be free from visual and functional defects after cyclical preconditioning (variant 1, 6 cycles and upper temperature +55±2℃)	7.5	Yes	
Injection shall be completed in cool atmosphere (+5±3℃).	7.6	Yes	
Injection shall be completed in hot atmosphere (+40±2℃, 50±10%RH).	7.7	Yes	

2.3 Usage and durability requirements

Requirement(s)	Equivalent item in DIR 0154-010	Included in GP2017 Design verification (Yes/No)	Justification for exemption
The shelf life of components shall be at leas (b) (4) years when stored in temperatures between (b) (4)	8.1	No	This property is not influenced by the difference of the 3 components and pre-filled syringe content. The design differences compared to GP2015 (b) (4) re: 1. Plunger spring 2. Plunger Rod 3. Rear End Cover. The Plunger spring was subject to all relevant durability tests in the course of (b) (4) refer to test report#0154-004-ATR-T001). The Plunger Rod and Rear End Cover have only been changes regarding (b) (4) The material is identical to (b) (4) which has also been subject to all relevant durability tests (refer to test report ##0154-004- ATR-T001). It is considered that the (b) (4) has no impact on the durability of the device. Consequently the durability requirements #0154-011-IR-S003 Rev 1.0 are considered covered by test report #0154-004- ATR- T001)
The shelf life of front and rear subassembly shall be at least (b) (4) years when stored in temperatures between (b) (4) (b) (4)	8.2	No	
The shelf life of the assembled device shall be at leas (b) (4) years when stored in temperatures between (b) (4)	8.3	No	

Additional Verification data referenced in MAF performed by Sandoz: *[Module 3.2.R Technical summary (b) (4) device - Attachment 4]*

1) Final device functional test (T=23±5°C, RH: 50±25%)

Item	Test Name	Output/ unit	DIR item (0154-011-IR-S003r1.0)	Testing instruction	Specification limit	Amounts
Test 1	Injection time	sec.	#4.1	0154-002-TI-F013r4.0	The injection time in air shall be less or equal to (≤) (b) (4) seconds.	60pcs (with label)
	Dose accuracy	ml	#4.2		The delivered volume shall be equal or larger than (≥) (b) (4) ml calculated according to the dose accuracy requirements specified in ISO11608-1 ((D1, N=60, one side tolerance limit factor k at 95% CI with 0.975P)	

Statistical Value	Injection Time (sec.)	Dose Accuracy (ml)
Mean	*4*	*0.817*
Max.	*5*	*0.828*
Min.	*3*	*0.787*
StDev.	*0.49*	*0.0074*
Result	*PASS*	*0.817-(2.384*0.0074)=0.799≥* (b) (4) *ml PASS*

2) Drop test (T=23±5°C, RH: 50±25%)

Item	Test Name		Output / unit	DIR item (refer to 0154-011-OT-S008r1.0)	Test instruction	Specification	Amounts
Test 2	Three directions	Visual inspection	Pass/ Fail	#7.2	ISO 11608-1:2012	The device shall be free from visual and functional defects after (b) (4) nm free fall testing.	60pcs (with label)
		Dose accuracy	ml		0154-002-TI-F013r4.0	➢ Each data must fulfil $\bar{x}$-(k*s) ≥ (b) (4) ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.950P. ➢ $K_{act} \geq k$	
		Injection time	sec.			≤ (b) (4) (All individual value within this limit)	

Visual Inspection After Drop Test	
Horizontal Direction	PASS
Cap Upward Direction	PASS
Cap Downward Direction	PASS

Horizontal Direction		
Statistical Value	Dose Accuracy (ml)	Injection Time (sec.)
Mean	*0.813*	*4*
Max.	*0.821*	*4*
Min.	*0.796*	*3*
StDev.	*0.0069*	*0.32*
Result	*0.813-(2.396*0.0069)=0.796≥* (b) (4) *ml* (b) (4) *(PASS)*	*PASS*

Cap Upward Direction		
Statistical Value	Dose Accuracy (ml)	Injection Time (sec.)
Mean	*0.815*	*4*
Max.	*0.824*	*4*
Min.	*0.803*	*3*
StDev.	*0.0060*	*0.40*
Result	*0.815-(2.396*0.0060)=0.801≥* (b) (4) *ml* (b) (4) *(PASS)*	*PASS*

Cap Downward Direction		
Statistical Value	Dose Accuracy (ml)	Injection Time (sec.)
Mean	*0.811*	*4*
Max.	*0.821*	*4*
Min.	*0.792*	*3*
StDev.	*0.0065*	*0.35*
Result	*0.811-(2.396*0.0065)=0.795≥* (b) (4) *ml* (b) (4) *(PASS)*	*PASS*

3) Environmental requirements

Item	Precondition and testing at	Test Name	Output/ unit	DIR item (refer to 0154-011-OT-S008r1.0)	Test instruction	Specification	Amounts
Test 3	Injection shall be completed in cool atmosphere (5±3℃).	Dose accuracy	ml	#7.6	ISO 11608-1:2012, 0154-002-TI-F002r02	➢ Each data must fulfil $\bar{x}-(k*s)\geq$ (b) (4) ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.975P. ➢ $K_{act}\geq k$	60pcs
	Injection shall be completed in warm atmosphere (40±2℃, 50±10%RH).			#7.7			60pcs

Statistical Value	Injection at Cool (5±3℃)	Injection at Warm (40±2℃, 50±10%RH)
	Dose Accuracy (ml)	Dose Accuracy (ml)
Mean	*0.821*	*0.811*
Max.	*0.835*	*0.823*
Min.	*0.801*	*0.788*
StDev.	*0.0091*	*0.0067*
Result	*0.82-(2.384*0.0091)=0.799≥* (b) (4) *ml* (b) (4) *PASS*	*0.811-(2.384*0.0067)=0.795* (b) (4) *ml* (b) (4) *PASS*

4) Storage environmental test

Item	Precondition	Test Name	Output / unit	DIR item (refer to 0154-011-OT-S008r1.0)	Test instruction	Specification	Amounts
Test 4	Injection shall be completed after subassemblies have been preconditioned for 96hours at 55±2℃ (50±10%RH).	Dose accuracy	ml	#7.3	ISO 11608-1:2012, 0154-002-TI-F002r02	➢ Each data must fulfil $\bar{x}-(k*s) \geq$ (b) (4)ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.975P. ➢ $K_{act} \geq k$	60pcs
	Injection shall be completed after subassemblies have been preconditioned for 96hours at -40±3℃.			#7.4			60pcs
	The sub-assemblies shall be free from visual and functional defects after cyclical preconditioning. (variant 1, 6 cycles and upper temperature 55±2℃)	Visual inspection	Pass/ Fail	#7.5	The sub-assemblies shall be free from visual and functional defects after cyclical preconditioning		60pcs
		Dose accuracy	ml		ISO 11608-1:2012, 0154-002-TI-F002r02	➢ Each data must fulfil $\bar{x}-(k*s) \geq$ (b) (4)ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.950P. ➢ $K_{act} \geq k$	

Statistical Value	Preconditioning after 55±2℃, 50±10%RH	Preconditioning after -40±3℃
	Dose Accuracy (ml)	Dose Accuracy (ml)
Mean	*0.821*	*0.821*
Max.	*0.833*	*0.832*
Min.	*0.796*	*0.801*
StDev.	*0.010*	*0.0069*
Result	*0.821-(2.384*0.010)=0.797≥* (b) (4)*ml* (b) (4) *PASS*	*0.8-(2.384*0.0069)=0.805≥* (b) (4)*ml* (b) (4) *PASS*

Statistical Value	Cyclical Preconditioning
	Dose Accuracy (ml)
Mean	*0.815*
Max.	*0.831*
Min.	*0.797*
StDev.	*0.0076*
Result	*0.815-(2.022*0.0076)=0.800≥* (b) (4)*ml* (b) (4) *PASS*

5) Transportation test (T=23±5℃, RH: 50±25%)

Item	Test Name	Output/ unit	DIR item (refer to 0154-011-OT-S008r1.0)	Test instruction	Specification	Amounts
Test 5	Package inspection	Pass/ Fail	#7.1	ASTM D4169-09	Refer to Note	2 cartons
	Product inspection					658pcs
	Dose accuracy	ml		0154-002-TI-F002r02	➢ Each data must fulfil $\bar{x}$-(k*s) ≥ (b) (4)ml Refer to ISO11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with 0.975P. ➢ K_{act} ≥k	30pcs
	Injection time	sec.			≤ (b) (4)ec. (All individual value within this limit)	

Package and Product Inspection		
Based on the inspection, the carton is still intact and there is no any defect on the tray and sample. Therefore, the package and product inspection are PASS.		
Statistical Value	Dose Accuracy (ml)	Injection Time (sec.)
Mean	*0.812*	*4*
Max.	*0.825*	*4*
Min.	*0.795*	*3*
StDev.	*0.0069*	*0.36*
Result	*0.812-(2.608*0.0069)=0.794≥* (b) (4)*ml* (b) (4) *PASS*	*PASS*

Reviewer Comment:

The verification testing provided is acceptable to ensure that the (b) (4)_GP2017_40 autoinjector meets its essential performance requirements when delivering the GP2017 drug in its intended use environment.

The sponsor provided appropriate justifications when using the (b) (4) or (b) (4) autoinjector devices.

Assessment by Sandoz:

Item	Test Name	DIR item (refer to 0154-011-OT-S008r1.0)	Test document #	Specification limit	Amounts
Test 7	Assessment by Sandoz project team	DIR 4.11, 4.12, 4.13, 4.14, 4.19, 4.22, 4.27, 4.29, 4.30, 4.31, 4.32, 4.33, 4.34, 4.35, 4.36, 4.38, 4.39, 10.2	Separate protocol 0154-011-VE- (TBD)	Pass/ Fail	5 pcs or as required

Reference ID: 4306205

DIR Item	Requirement	Evaluation/ Justification	Result
4.11	The device shall give an audible feedback at the start of the injection stroke.	These requirements are subject for project team assessment and verified [4].	PASS
4.12	The device shall give an audible feedback signalling "end of injection" as late in the injection stroke as practically possible.		PASS
4.13	The device shall have a visible end of injection indicator.		PASS
4.14	It shall be possible to monitor the Plunger Rod movement during the injection stroke.		PASS
4.15	The device shall allow for visual inspection of the drug product, i.e. the formulation and the pre-filled syringe.	No need to repeat the test in GP2017 Design Verification. Customized component for GP2017: rear end cover, plunger rod, and plunger spring does not influence the listed functional performance requirements [2]. Nor does the content of the pre-filled syringe pose an impact to the listed requirement [2]. The device performance is already verified within (b) (4) design verification test [7].	PASS
4.16	The separation force between the Cap and the RNS Remover shall be (b) (4)		PASS
4.17	The separation force between the RNS Remover and the RNS shall b (b) (4)		PASS
4.18	When the Cap is twisted off from the device, any potential rotation of the RNS may not cause coring (cut out of rubber particles).		PASS
4.19	The needle must be hidden before use.	Subject for project team assessment and verified [4].	PASS
4.20	The rotation torque should b (b) (4) when twisting off the Cap from device with label.	No need to repeat the test in GP2017 Design Verification [2]. The device performance is already verified within (b) (4) design verification test [7].	PASS
4.21	The separation force between the Cap and the Front end cover (plastic parts only) shall be (b) (4) (b) (4)		PASS
4.22	The noise level and tactile response during activation and injection shall be acceptable by the customer.	Subject for project team assessment and verified [4].	PASS

DIR Item	Requirement	Evaluation/ Justification	Result
4.23	The syringe needle shield must not be moved outwards from the syringe during handling/ assembly in a way that the needle is exposed to microbiological contamination.	No need to repeat the test in GP2017 Design Verification [2]. The device performance is already verified within (b) (4) design verification test [7].	PASS
4.24	The assembly of the PFS must be facilitated by sufficient guiding and chamfers in Front sub-assembly.		PASS
4.25	The overall weight of the device, including filled 1 ml syringe, must not exceed (b) (4)	Test result well within specification [3, 5].	PASS
4.26	(b) (4)	No need to repeat the test in GP2017 Design Verification [2]. The dimensions are already verified within (b) (4) design verification test [7].	PASS
4.27	The device must automatically insert the needle and inject the medication.	Subject for project team assessment and verified [4].	PASS
4.28	The design of the device shall be adopted for delivery of one dose with Pre filled syringe fill volume lower thar (b) (4)	This requirement is a carry-over item from (b) (4) project and has been verified in [7, 12].	PASS
4.29	The device must comprise no more than two sub-assemblies that are to be assembled with the pre-filled syringe in a final assembly step.	Subject for project team assessment and verified [4].	PASS
4.30	The device must have a triangular cross section, as described in the Industrial design report.		PASS
4.31	The outer shape of the device must not have any sharp edges.		PASS
4.32	The body of the device must have a straight shape, without curves.		PASS
4.33	The device must be actuated by pressing the needle cover against the injection site only, without additional trigger button.		PASS
4.34	The device must have a protective Cap, to be removed prior to injection.		PASS

DIR Item	Requirement	Evaluation/ Justification	Result
4.35	The Cap must be possible to remove by a rotational movement, using a cam curve as described in Industrial design report.	Subject for project team assessment and verified [4].	PASS
4.36	The device must have a needle cover that locks in its outer position, protecting the needle, after injection.	Item defined to assess by project team but it was assessed during attribute test for GP2015 (b) (4) 0 [13]. Both GP2015 (b) (4) 50 and GP2017- (b) (4) 0 has the same Needle Cover Spring that locks the Needle Cover after completion of dose delivery, thus the result is deemed not to be affected by the difference in Rear End Cover, Plunger Rod or Plunger Spring. Thus, the requirement is considered verified as part of [13].	PASS
4.37	The device shall be free from visual and functional defects after vibration testing according to ISO 11608-1:2012.	No need to repeat the test in GP2017 Design Verification [2]. The requirement is already verified in vibration test [9, 10].	PASS
4.38	Front subassembly: Cap (b) (4) Needle cover extension (b) (4) Front end cover (b) (4) Rear subassembly: Plunger rod (b) (4) Rear end cover (b) (4)	Subject for project team assessment and verified [4].	PASS
4.39	The cap must be designed to prevent accidental activation when removed and the user must not be able to activate the device without removing the cap.		PASS

Reviewer Comment:

The referenced testing (performed by Sandoz) could not originally be found in the BLA. Design Verification Master Report 0154-011-VE-T002 can be found referenced in the BLA document (b) (4) GP2017_40_DVERSR_02 but is not included in either the MAF or the BLA. This is information was provided

after interactive review.
The documents are acceptable.

Shipping Validation (from technical summary in 3.2.R):
Shipping functional testing appears to be acceptable, results are included in test reports/protocols 0154-011-TP-T002 and 0154-011-TR-T002.

Table 9-5 Functional testing of (b) (4) GP2017_40 after mechanical stress testing

Attribute	Specification	2 pack presentation stressed	3x2 pack presentation stressed
Dose accuracy	(b) (4)	0.800 mL	0.804 mL
Appearance of autoinjector		Complies	Complies
Identity of syringe ring label		Complies	Complies
Cap removal torque		0.4 Nm	0.4 Nm
Activation force		8 – 10 N	8 – 9 N
Needle cover displacement at activation		5.5 – 5.6 mm	5.5 – 5.6 mm
Injection time		7 s	6 s
Injection depth		7.8 – 8.5 mm	7.7 – 8.4 mm
Needle cover safety displacement at (b) (4)		0.8 mm	0.8 mm
Rear end cover displacement at (b) (4)		0.4 mm	0.3 mm

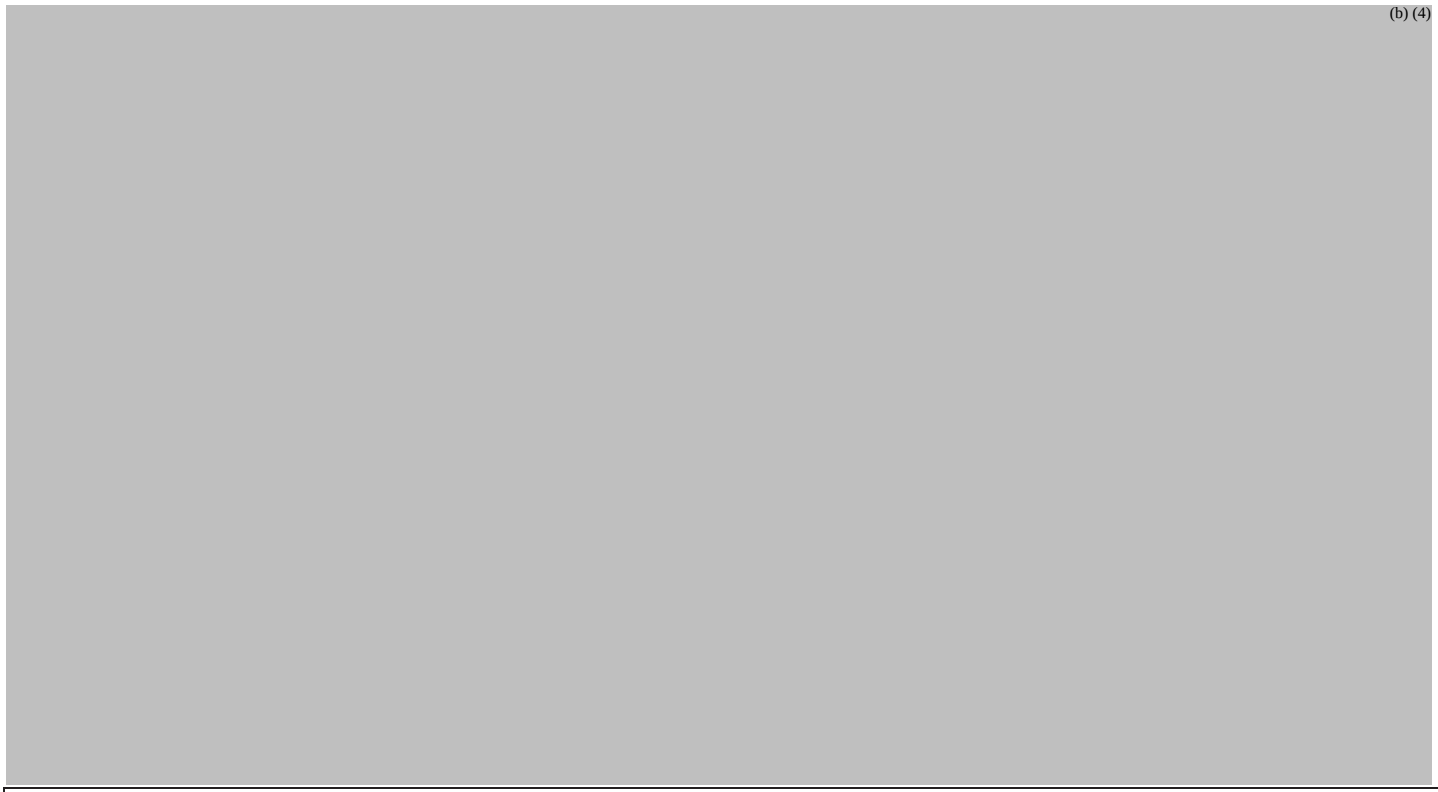
4.3. RISK ANALYSIS

The sponsor provided the following table with regards to the risk analysis activities:

Table 3-2 Risk analysis, risk evaluation and risk control documents

Document Title	Document No.
Hazard Identification List	(b) (4) GP2017_40_HID
Hazard Identification Checklist (b) (4)	0154-011-RM-S003
Application/Usability Risk Assessment	(b) (4) GP2017_40_RA-Ap
Application Specification	GP2017_40_ASPEC
Usability Specification	GP2017_40_USPEC
Primary Operating Functions	GP2017_40_POF
Design FMEA (b) (4)	0154-011-RM-S002
Process FMEA SKD 2 (b) (4)	GP2017 (b) (4) 40 SKD2 SAAM FMEA-0154K-E001
Process FMEA SKD 3	(b) (4) 02B SKD3 SAAM FMEA-0154G-E002
Process FMEA SKD 4	(b) (4) 01A SKD4 SAAM FMEA-0154B-E010
Process FMEA SKD 5	(b) (4) 01A SKD5 SAAM FMEA-0154B-E009
Process FMEA SKD 6 SAAM1 (b) (4)	(b) (4) SKD6 SAAM FMEA-0154B-E005 (b) (4)
Process FMEA SKD 6 SAAM2	(b) (4) SKD6 SAAM FMEA-0154B-E007 (b) (4)
Process FMEA SKD 6 SAAM3	(b) (4) SKD6 SAAM FMEA-0154B-E014 (b) (4)
Process FMEA (b) (4) roduct assembly (clinical batch)	(b) (4) GP2017_40_RA-PR
(b) (4) Auto-Injector Assembly Process FMEA (b) (4) (b) (4)	RA-140-101-15-12-001
(b) (4) Auto-Injector Assembly Process FMEA Summary Report (b) (4)	RA-140-101-15-12-003
Risk Estimation & Evaluation Report (b) (4)	0154-011-RM-S004

Addtionally, after request of additional information, the sponsor provided the following uFMEA document (RA-Ap): (a representative screenshot is provided)



Reviewer Comment:
After additional information was provided, the risk analysis was determined to be acceptable.

4.4. DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent:

From pg. 18 of MAF (b) (4):

Table 5. Sub-assembly Release testing performed by (b) (4)

Test	Specification
Cap Removal Torque	≦ (b) (4)
Activation Force	(b) (4)
Dose Accuracy	$\bar{x} - (k \cdot s) \geqq$ (b) (4) one side tolerance limit factor k at 95% CI with 0.975P
Injection Depth	(b) (4)
Needle Cover Safety Displacement at (b) (4)	Max. displacement: (b) (4)
Needle Cover Displacement before Activation	(b) (4)
Injection Time	(b) (4)

Reviewer Comment:
The release specifications/testing are adequate.

5. INFORMATION REQUESTS – SENT 04/10/2018

5.1. Information Requests for Sponsor (Sandoz)

1. In your device risk management document, (b) (4)-GP2017_40_RMUER_02 ("Risk Management and Usability Engineering Report") you state the following with regards to the risk analysis: "Hazard identification, risk estimation and evaluation for the device constituent part of the combination product have been carried out by (b) (4) according to their internal procedures, in collaboration with and with the final approval of Sandoz. Hazard Identification Checklist, (b) (4) Design-FMEA and (b) (4) Process FMEAs have been used as input to the risk estimation & evaluation report." The information provided in this document does include adequate risk analysis documentation to ensure all the hazards associated with the device have been identified, evaluated, and mitigated. The FDA Guidance Document, "Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products," (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf) recommends that you conduct a risk analysis that considers the overall product and includes both the injector and drug/biological product for injection. Specifically, you should assess the risk of use of the intended drugs/biological products delivered with the injector as related to the human factors characteristics of the patient population using the intended drugs/biological products. It is not clear if the risk analysis performed by (b) (4) and approved by Sandoz incorporates recommendations for the risk analysis per FDA Guidance. Multiple documents are referenced in Table 3-2 of Document (b) (4)-GP2017_40_RMUER_02 that may include this information, but were not included in the BLA submission. If the documents referenced in Table 3-2 incorporate the above recommendations, provide these documents. If these recommendations have not been addressed, provide updated risk analysis documentation that includes the full identification, evaluation and mitigation of all hazards associated with the device, and provide any additional verification documentation as necessary.

   Sponsor Response to IR 1:
   The appropriate assessment that evaluates the risks users face when using the (b) (4)- GP2017_40 - according to the Instruction for Use is provided in Table 3-2 of Document (b) (4) GP2017_40_RMUER_02 as "Application/Usability Risk Assessment; (b) (4)-GP2017_40 RA-Ap". This document is now provided as [Attachment3– (b) (4)-GP2017_40_RA-Ap].
   A complete summary of human factors engineering activities has been already provided in the BLA (please refer to [Module 3.2.R Technical summary (b) (4) device–attachment2]).

   Reviewer Comment:

The updated risk analysis documentation is acceptable.

The sponsor also provided updated user requirement specification documents and traceability matrices that completes the design control aspect of the risk documentation.

2. You have referenced a multitude of SNZ documents in Design Verification Summary Report ((b) (4) GP2017_40_DVERSR_02) that are not included in the submission. The user requirements specifications ((b) (4)-GP2017_40_URS), (b) (4)-GP2017_40 Product Description ((b) (4)-GP2017_40_PRDESC), Traceability Matrix for (b) (4)-GP2017_40 ((b) (4)-GP2017_40_TRAMA) are referenced to include critical design control information yet cannot be found in the eCTD. Provide these documents.

Sponsor Response to IR 2:
The requested documents are provided as attachments to this response document. Please refer to [Attachment 6-(b) (4)-GP2017_40_URS], [Attachment 7–(b) (4)-GP2017_40_URS_(b) (4)], [Attachment 8 -(b) (4)-GP2017_40_PRDESC] and [Attachment 9 -(b) (4)- GP2017_40_TRAMA]

Reviewer Comment:
The sponsor provided this information, and it is reviewed in Section 4.2 of this memo.

The information was determined to be adequate.

3. The documents, "0154-011-VE-T002" (Design Verification Master Report) and "0154-011-VE-T002," (Design verification protocol for Assessment by project team for GP2017-(b) (4)-40) are referenced Section 8 of document (b) (4)-GP2017_40_DVERSR_02 (Design Verification Summary Report) submitted under module 3.2.R of BLA 761071. These documents are also referenced in MAF(b) (4) as testing performed by Sandoz to verify the Design Input Requirements 4.11, 4.12, 4.13, 4.14, 4.19, 4.22, 4.27, 4.29, 4.30, 4.31, 4.32, 4.33, 4.34, 4.35, 4.36, 4.38, 4.39, and 10.2 have been met. These complete documents were not included in the BLA, nor was it provided in the Master File. Provide these aforementioned test protocols and reports to ensure the (b) (4)-GP2017_40 meets its design input requirements and is safe and effective for use.

Sponsor Response to IR 3:
The requested documents are provided as attachments [Attachment4 -0154-011-VE-T002] and -[Attachment5– 0154-011-VE-S002] to this response document.

Reviewer Comment:
The sponsor provided this information, and it is reviewed in Section 4.2 of this memo.

The information was determined to be adequate.

4. You state the following in 3.2.R Technical Summary (b) (4) Device (722-1263-32r-tech-sum-(b) (4)-dev-790-2-0) with regards to device shelf life of the autoinjector device: "Shelf life was determined by (b) (4) using accelerated aging studies. The aged samples were inspected and tested via visual inspection and functional tests, and met the performance requirements. Detailed information on the aging tests performed is presented in the MAF-(b) (4)." This testing provided in MAF (b) (4) referenced was deficient and did not adequately demonstrate the device meets a shelf life of (b) (4) years. An information request will be sent to the MAF holder, (b) (4) to resolve this deficiency.

Sponsor Response to IR 4:
Sandoz acknowledges that a deficiency letter will be sent directly to the MAF holder (b) (4) and has also informed the MAF holder to expect it.
However, to avoid any potential misunderstandings, Sandoz would like to clarify that"…the device meets a shelf life of (b) (4) years" is not correctly representing the claim made in the submitted BLA. [Module3.2.R Technical summary (b) (4) device, Section4.8.2] states:
"The shelf life of GP2017-(b) (4)_40 auto injector subassemblies prior to final assembly is (b) (4) years and after final assembly it is (b) (4) years, thus providing for a maximum shelf life of (b) (4) years.
Shelf life was determined by (b) (4) using accelerated aging studies. The aged samples were inspected and tested via visual inspection and functional tests, and met the performance requirements. Detailed information on the aging tests performed is presented in the MAF-(b) (4)."

Once these two sub-assemblies have been assembled with a syringe, the shelf life of the assembled product is maximally (b) (4) years. However, the actual shelf life of the final assembled product is depending on the shelf life of the drug product filled in the syringe. For GP2017, the shelf life of the GP2017 bulk pre-filled syringe as claimed in the submitted BLA is 24months when stored at intended storage conditions. For the shelf life of the finally assembled combination product (b) (4)-GP2017_40, [Module 3.2.R Technical summary (b) (4) device, section4.8.3]states: "The defined shelf life of the final, assembled (b) (4)-GP2017_40 is based on the shelf life of the drug product constituent part as described in [Module 3.2.P.8.1]. The combination product has to be stored at36°F to 46°F (2°C to 8°C)."

Therefore, a shelf life of (b) (4) years for the device as stated in the question reflects the combined shelf life of the device components before final assembly ((b) (4) years)and the shelf life of the assembled device after final assembly (b) (4) years). However, as stated in the submitted BLA and explained above, the actual shelf life of the marketed combination product (b) (4)-GP2017_40 is based on the shelf life of the drug product constituent part, which is 24 months.

Reviewer Comment:
This issue is discussed further under the Information Requests for MAF Holder ((b) (4)).

5.2. Information Requests for MAF Holder ((b) (4))

1. You have included in Attachment 4 of MAF (b) (4) an accelerated aging test protocol and report for the (b) (4) autoinjector platforms as substitution for the GP2017-(b) (4)-40 autoinjector system. While this testing appropriately demonstrates the functionality of the device components that are identical between the (b) (4) device and the GP2017-(b) (4)-40 device, it does not demonstrate functionality where they differ, most notably dose accuracy and injection time. While the test protocols described in 0154-004-ATR-T001 for dose accuracy and injection time are acceptable, they are not applicable to the GP2017-(b) (4)-40 as the device delivers 0.8mL of fluid and does not have an identical plunger rod. Please repeat the aging verification testing described in 0154-004-ATR-T001 for dose accuracy and injection time using the final finished GP2017-(b) (4)-40 device.

MAF Holder Response to IR 1:

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

In addition to the design verification I aging program performed by (b) (4) Sandoz has performed stability testing using the marketable GP201 7-(b) (4) device combination product including GP2017 filled syringes. This stability testing has been perfo1med on batches assembled in the comse of the assembly-and packaging process validation at (b) (4) and includes dose accuracy and injection time testing.

To facilitate the review by the agency, available Sandoz stability results are provided below in Tables 2-1 and 2-2 to support (b) (4) response. All results fulfilled the acceptance criteria.

Table 2-1 Functional testing results for (b) (4) GP2017_40 at intended storage condition (testing performed by Sandoz)

Testing attribute	Batch #016C16A					Batch #017C16A					Batch #018C16A				
	Pull points [months]					Pull points [months]					Pull points [months]				
	0	6	9	12	18	0	6	9	12	18	0	6	9	12	18
Dose accuracy (b) (4)	0.782	0.783	0.794	0.798	0.792	0.793	0.795	0.800	0.798	0.789	0.799	0.800	0.804	0.804	0.797
Injection time (b) (4)	7	6	6	6	5	6	6	6	6	5	8	6	6	7	5

Table 2-2 Functional testing of (b) (4) GP2017_40 at the accelerated storage condition (testing performed by Sandoz)

Testing attribute	Batch #016C16A		Batch #017C16A		Batch #018C16A	
	Pull points [months]					
	0	6	0	6	0	6
Dose accuracy (b) (4)	d.i.c.	0.797	d.i.c.	0.796	d.i.c.	0.803
Injection time (	d.i.c.	7	d.i.c.	7	d.i.c.	7

*. d.i.c.: done with intended condition, please refer to Table 2-1.

Reviewer Comment:
Based on the near identical nature of the spring component and rear assembly of the (b) (4) and (b) (4) GP2017-40 devices, the rationale presented here for age-dependent degradation of function is acceptable. Additionally, no notable differences were found in the devices during the rigorous design verification testing and comparison of the (b) (4) and GP2017-40 devices.

Sandoz provided dose accuracy and injection time testing at 18 months, 6 months short of the intended shelf life of 24 month. This information, in combination with the age-degradation rationale, are acceptable to demonstrate the shelf life of the device.

The response adequately addresses the agency's concerns.

6. OUTSTANDING DEFICIENCIES

None.

7. POST-MARKET COMMITMENTS/POST-MARKET REQUIREMENTS

None.

8. RECOMMENDATION

Autoinjector component of combination product approvable for use with GP2017.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHUONG N TON
08/13/2018
Administratively checked into DARRTS by Project Manager on behalf of the reviewer

Clinical Inspection Summary

Date	July 6, 2018
From	Bei Yu, Ph.D., Reviewer Janice Pohlman, M.D., M.P.H., Team Leader Susan D. Thompson, M.D. for Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Nina Ton, Regulatory Project Manager Gary Chiang, M.D., Clinical Reviewer David Kettl, M.D., Clinical Team Leader Division of Dermatology and Dental Products (DDDP)
BLA #	761071
Applicant	Sandoz, Inc
Drug	GP2017, a proposed biosimilar to Humira (adalimumab)
NME	No
Review Priority	Standard Review
Proposed Indication	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis (JIA) in patients 4 years of age and older, Psoriatic Arthritis (PsA), Ankylosing Spondylitis (AS), Adult Crohn's Disease (CD), Ulcerative Colitis (UC), Plaque Psoriasis (PsO)
Consultation Request Date	January 19, 2018
Summary Goal Date	July 6, 2018
Action Goal Date	Oct 30, 2018
BsUFA Date	Oct 30, 2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Berenguer and Weinberg were selected for inspection in support of BLA 761071. Dr. Berenguer's site was unable to be inspected because of a fire that had occurred at the site in August 2016 in which all study source documents with the exception of study documents in the regulatory binder were destroyed by fire or water damage. OSI requested and subsequently reviewed select monitoring reports and all correspondence between the sponsor, the monitoring contract research organization (CRO), and Dr. Berenguer's site related to the study and reported fire. Another clinical investigator site, Dr. Wallace, was selected as a replacement inspection site for Dr. Berenguer.

The preliminary compliance classification for the inspection of Drs. Weinberg and Wallace is Voluntary Action Indicated (VAI). While regulatory violations were observed at Drs. Weinberg and Wallace's sites as described below, they do not have a significant impact on data reliability. Based on the results of these inspections, the study appears to have been conducted

adequately, and the data generated by these sites appear acceptable in support of the respective indication.

OSI is unable to verify the source data from Dr. Berenguer's site due to a fire. Because selection of this site for inspection by the review division was due to relatively low response rates compared to other participating study sites and additional information described below, the review division may wish to perform a sensitivity analysis to see if data from this site has significant impact on data analysis outcome.

II. BACKGROUND

The Applicant submitted this biosimilar BLA to support the use of GP2017, a recombinant human monoclonal antibody against Tumor Necrosis Factor (TNF) α, for the treatment of all indications approved for the reference product US-Humira®. Inspections were requested for the following protocol in support of this application:

GP17-301, entitled "A randomized, double-blind, multicenter study to demonstrate equivalent efficacy and to compare safety and immunogenicity of a biosimilar adalimumab (GP2017) and Humira® in patients with moderate to severe chronic plaque-type psoriasis"

The study was conducted at 73 clinical sites in the U.S. and Europe between December 2013 and February 2016. A total of 465 subjects were enrolled.

This was a multi-center, randomized, double-blind, Phase 3 study. Eligible subjects were randomized in a 1:1 ratio into one of two treatment groups, either GP2017 or Humira. Both treatment groups received s.c. GP2017 or Humira® as a loading dose of 80 mg at Visit 2 and subsequently every other week (qow) for 8 doses. Assessments for the primary endpoint (PASI 75 response) were done at Week 16 for both treatment arms prior to the next dose at Week 17.

The primary efficacy endpoint was:
PASI 75 response rate (proportion of subjects showing at least a 75% improvement PASI (Psoriasis Area and Severity Index) at Week 16 in Treatment Period 1)

Rationale for Site Selection:

Initially, two clinical sites (Drs. Berenguer and Weinberg) were selected due to high enrollment. In addition, the efficacy results from Dr. Berenguer's site were influential and different from other sites (low response rates and unusually low variability within the site). Due to an accidental fire at Dr. Berenguer's site, all source documents were destroyed. Dr. Wallace's site (Site 1233) was added on as a replacement site for Dr. Berenguer based on the medical team's request.

III. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol # / # of Subjects Enrolled	Inspection Dates	Compliance Classification
Site #1268 Ramon A. Berenguer, MD Florida Medical Center and Research, Inc. Miami, Florida, 33142	GP17-301 Subjects: 33	6 - 7 March 2018	All source documents were destroyed in a fire accident.
Site #1218 Jeffrey Mitchell Weinberg, MD Forest Hills Dermatology Group 103-11 68th Dr., Ste. L1 Forest Hills, New York, 11375	GP17-301 Subjects: 18	19 - 23 April, 2018	VAI*
Site #1233 Paul W. Wallace, MD Wallace Medical Group, Inc., 8920 Wilshire Blvd. Suite 327 Beverly Hills, CA 90211	GP17-301 Subjects: 18	4 – 8 June, 2018	VAI*

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
* Pending: Classification is preliminary pending receipt of the EIR and issuance of correspondence to the inspected entity. An addendum to the Clinical Inspection Summary will be issued if the finalized EIR differs significantly from the draft EIR received from the ORA investigator.

Clinical Investigator Sites

1. Ramon A. Berenguer, M.D.

The ORA investigator was unable to conduct an inspection at the site because study source documents for Study GP17-301 were destroyed by a fire at the site on August 1, 2016. The ORA investigator interviewed Dr. Berenguer who stated that all study procedures had been completed at the time of the fire. Dr. Berenguer had sent a letter to the Sponsor detailing the fire and the status of the study documents on Sep 28, 2016. The ORA investigator obtained a certified copy from the Miami fire department stating that the fire at the clinical research facility on August 1, 2016 was considered to be accidental and due to electrical malfunction. The ORA investigator also obtained a copy of the letter that Dr. Berenguer sent to the sponsor, Sandoz, describing the fire as resulting from addition of new office equipment that overwhelmed the electrical system of the building. Also noted in this letter was that the computer servers were destroyed in the fire and there was no backup system.

OSI subsequently requested information from the sponsor regarding all monitoring reports for this site, as well as all correspondence between the sponsor, the monitoring contract research organization (CRO), and the clinical investigator and study site staff related to the fire accident.

Based on the sponsor's response to the information request that was submitted to the BLA on May 31, 2018, the CRO's audit team was notified about the fire by the site on Aug 2, 2016 via email, one day prior to a scheduled audit on Aug 3, 2016. An email dated Aug 23, 2016, outlining a sponsor internal discussion indicates a decision by the sponsor to include the site's data in the BLA. On August 25, 2016, the sponsor reported the fire incident to the FDA in the cover letter of the original BLA submission and also in a submission to IND 115732.

The sponsor's response notes that two types of monitoring visits were executed by the CRO, (b) (4). Blinded Monitoring Visits were carried out to review activities of blinded site staff. In addition, unblinded Pharmacy Visits were conducted to review site staff activities related to handling of Investigational Product. Monitoring visits started with a site selection visit on Aug 27, 2014, and a site initiation visit on Oct 14, 2014 to Close-Out-Visit (via telephone) on Dec 5, 2016. In addition to site selection, site initiation visits, and close-out visit, there were total of 15 interim visits (blinded monitoring visits) conducted approximately every 6 weeks, and 7 pharmacy visits, including the close-out-visit of pharmacy on June 29-30, 2016.

Several monitoring reports were randomly selected by OSI for review including monitoring visits conducted on Jun 28, 2016 (the last visit prior to the fire incident), May 28-29, 2015, June 4-5, 2015, and July 16-17, 2015. During monitoring visits, the monitor accessed the following documents at the site to verify the accuracy of information and compliance to the protocol: e.g., case report form and patient diary, central lab, IVRS documentation, medical charts/source documents for each subject, delegation log, and investigator's site file with all regulatory documentation. No major GCP noncompliance issues were noted.

OSI Reviewer Comment: OSI had received several complaints about this site in 2016; however, the complaints were not specific to the study conducted under this IND. Complaints from two different sponsors indicated potentially significant problems with clinical study conduct at this site. NON-RESPONSIVE

The Office of Regulatory Affairs was unable to conduct an inspection related to these complaints because of the destruction of most study-related records in the fire of August 1, 2016.

OSI is unable to verify source data at this site for the study submitted in support of the BLA. Since the review division selected this site for inspection due to high enrollment and response rates that appeared to be lower than was observed for other sites, OSI is recommending that the review division conduct appropriate sensitivity analyses with and without data from this site to see if there is significant impact on study outcome.

2. Jeffrey Mitchell Weinberg, M.D.

At this site for Protocol GP17-301, 26 subjects were screened and 18 were enrolled, 13 of whom completed the study. The informed consent forms for all 18 enrolled subjects were reviewed to ensure that subjects were properly consented.

A comprehensive review was completed for all 18 of the subjects enrolled at this site to confirm compliance with the protocol. The source documents were compared against the sponsor line listings provided in the assignment background material, specifically the following listings: PASI (Psoriasis Area and Severity Index), IGA (Investigator Global Assessment) Response, Demographic Information, Disposition, Protocol Deviations, Adverse Events, and Concomitant Medications. The sponsor's line listing of PASI and IGA Response were compared against the enrolled subjects' (18) source records; no discrepancies were observed. SAEs and AEs were accurately documented and reported; no evidence of under-reporting of adverse events was discovered.

An FDA Form 483, Inspectional Observations, was issued at the conclusion of the inspection for the Study GP17-301. Observations included:

- The site did not follow the protocol-required procedure, specifically for the following protocol deviations: One subject (Subject (b) (6)) did not have a serum pregnancy test done at rescreening; One subject (Subject (b) (6)) was not on a stable dose of concomitant treatment (meloxicam and enalapril) for four weeks prior to their first study treatment administration. These were reported to the BLA as protocol deviations.
- The site did not maintain adequate eCRFs, specifically,
    - Concomitant medications for Subject (b) (6) (amlodipine 5 mg oral, QD for hypertension started on (b) (6); and hydrochlorothiazide, 12.5 mg oral QD for hypertension started on (b) (6)) were noted in subject source records, but were not in eCRFs and data line listings;
    - Six subjects were not correctly stratified at randomization: Subjects (b) (6) (b) (6). These discrepancies were reported as protocol deviations. The site stated that the most of these six subjects were incorrectly stratified due to how their weights were entered in the system (lbs vs. kg). The monitor notified the site about this discrepancy much later, after the subjects had been randomized. These subjects weren't discontinued from the study.

In addition, two subjects were noted to have been enrolled and treated although they appeared to have signs of hypertension:

Subjects (b) (6) and (b) (6) were both enrolled and treated even though they had signs of hypertension, at screening (155/102 for Subject (b) (6), and 139/98 for Subject (b) (6)). The study coordinator explained that the sponsor stated that although the protocol says >160/>95 (Exclusion Criteria 9), to them that meant that a subject with both systolic and diastolic greater than or equal to 160/95 would be excluded, not with one of these values being too high.

The observations at this site appear to be minor and isolated in nature and unlikely to impact on efficacy and safety assessments for this study.

3. Paul W. Wallace, M.D.

At this site for Protocol GP17-301, 19 subjects were screened, and 16 subjects were enrolled and completed the study. The informed consent forms for all enrolled subjects were reviewed to ensure that subjects were properly consented. Primary efficacy endpoint data for all enrolled subjects were compared between source documents and data line listings, seven of whom were reviewed for entire study progress.

The primary efficacy endpoint data were verifiable. No evidence of under-reporting of adverse events was discovered.

An FDA Form 483, Inspectional Observations, was issued at the conclusion of the inspection for the Study GP17-301. Observations included:

- An investigation was not conducted in accordance with the signed statement of investigator: for example, study assessments for physical examination, vital signs, and weight were not performed during Visit 4 ((b) (6)) for Subject (b) (6) based on the protocol. This deviation was not reported in data line listings.
    - Based on the CI's response, the subject visited the site on (b) (6), one day early (out of window) for Visit 3 (Week 1) on (b) (6). The site performed all Visit 3 procedures except for drug administration. The subject visited the site on (b) (6). The site performed all Visit 4 procedures. However, based on the Sponsor's instruction, the site made an adjustment to re-label the visit conducted on (b) (6) as an unscheduled visit (instead of Visit 3) and re-label the visit conducted on (b) (6) as Visit 3 (instead of Visit 4) and administer study drug. The site failed to report this deviation.

- Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically:
    - PASI scores (Scaling) for the following subjects were not accurately documented in the eCRF from the source records:

		Scaling of PASI Score		
Subject	**Visit Date**	**Area**	**Source**	**Data Listing**
(b) (6)	(b) (6) (V4)	Head/Neck	2	4
	(b) (6) (V4)	Head/Neck	3	2
	(b) (6) (V9)	Head/Neck	3	2

- The IGA score for one subject was not been accurately documented in the eCRF from the source records:

			IGA Score	
Subject	**Visit Date**	**N/A**	**Source**	**Data Listing**
(b) (6)	(b) (6) (V4)	N/A	2	3

OSI Reviewer's Comment: These PASI and IGA assessments were performed at V4 (Week 3) and V9 (Week 13), not at Week 16 used for assessing the primary endpoint and appear to be isolated minor transcription errors and unlikely to significantly impact primary efficacy assessment.

- For Subject (b) (6), Clobetasol 0.05% cream (BID) was documented within a follow-up progress note ((b) (6)) in the attached medical chart, when the subject was also seen for V6 (Week 7). This medication has only been reported in eCRF with a stop date of (b) (6) (V1), but source records did not provide evidence the medication was re-started after V1.

OSI Reviewer Comment: Topical corticosteroids of moderate or greater potency were prohibited during the study period. This appears to be an isolated occurrence. In his written response to the Form FDA 483, the CI noted that Clobetasol was routinely written by the CI's medical assistant on the practice office chart and was pending CI's approval. But, the CI did not sign and approve restarting the medication or provide the prescription.

- Investigational records were not retained for a period of two years following approval of a drug's marketing application and discontinuance of the investigation and notification of FDA:

  - IVRS documentation for screening, randomization, and/or investigational drug allocation had not all been retained for subjects enrolled in the study.

  - Correspondence (e.g., emails, telephone logs, and lab communications from central lab) had not been maintained in the study records and were not accessible for review.

OSI Reviewer Comment: Many of the IVRS documents with investigational drug allocation numbers were not retained by the unblinded study staff during the initial study treatment period. However, the unblinded staff did record drug allocation numbers on investigational product administration sheets and the sponsor was able to provide documentation for the ORA investigator that subjects received the product to which they had been randomized.

Dr. Wallace provided an adequate written response to the FDA 483 observations on June 26, 2018.

Although regulatory violations were observed at this site, the observations appear unlikely to significantly impact primary efficacy or safety assessment for the study.

{See appended electronic signature page}

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/s/

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07/06/2018

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07/06/2018

SUSAN D THOMPSON
07/06/2018

M E M O R A N D U M

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

DATE: April 27, 2018

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

FROM: Mohsen Rajabi Abhari, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE
OSIS

THROUGH: Charles Bonapace, Pharm.D.
Director
DNDBE
OSIS

SUBJECT: Surveillance inspection of Hexal AG, Oberhaching, Germany.

Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an inspection of study GP17-104 (Hexal studies # BA 15021-R, BA 15020-R, and BA 16010-R) submitted to BLA 761071 conducted at Hexal AG, Oberhaching, Germany.

No objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

After reviewing the inspectional findings, we conclude the data from the audited studies are reliable. Thus, we recommend that the data from study GP17-104 and other studies using similar methods be accepted for further Agency review.

Inspected Studies:

BLA 761071

Study Number: **GP 17-104**
Study Title: "A randomized, double-blind, single-dose, three-arm parallel trial to determine the pharmacokinetics and safety of GP2017, EU-authorized Humira® and US-licensed Humira® following a single subcutaneous injection in healthy male subjects."

Dates of Bioanalytical PK study BA 15021-R conduct: 1/13/2016 – 6/24/2016

Dates of Bioanalytical ADA study BA 15020-R conduct: 1/11/2016 – 7/6/2016

Dates of Bioanalytical Nab study BA 16010-R conduct: 4/5/2016 – 8/3/2016

Analytical site: Hexal AG, Oberhaching, Germany.

OSIS scientists Mohsen Rajabi Abhari and Arindam Dasgupta audited the analytical portion of the above studies at Hexal AG, Oberhaching, Germany from 03/26/2018 to 03/29/2018.

The inspection included a thorough examination of study records, facility, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff.

At the conclusion of the inspection, we did not observe any objectionable conditions and did not issue Form FDA 483 to the analytical site. However, during the closeout meeting with Hexal's management, we discussed several items related to the selection of positive controls used during the conduct of the ADA study, BA 15020-R. These discussion items, however did not impact the reliability of the data generated in the ADA study.

Hexal responded to the discussion items on April 20, 2018 and acknowledged the findings (attachment 2). Hexal stated that they are (b) (4) (b) (4)

(b) (4)

Conclusion:

After reviewing the inspectional findings, we conclude the data from the audited studies are reliable. Therefore, I recommend that the data from study GP17-104 (Hexal studies # BA 15021-R, BA 15020-R, and BA 16010-R be accepted for further review). In addition, the data from studies using similar methods submitted to pending applications should be accepted for further Agency review.

Based on the inspectional findings, studies using similar methods conducted between the previous inspection (January 2016) and the end of the current Surveillance Interval should be accepted for review by the Agency without an inspection.

Mohsen Rajabi Abhari, Ph.D.
Pharmacologist, DNDBE/OSIS

Arindam Dasgupta, Ph.D.
Deputy Director, DNDBE/OSIS

Final Classification:

NAI– Hexal AG, Oberhaching, Germany.
FEI#: 3011617743

cc:
OTS/OSIS/Kassim/Choe/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Rajabi
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au

Draft: MR 04/11/2018; 04/24/2018 AD 04/18/2018; 04/25/2018
Edit: CB 04/20/2018; 4/27/2018

ECMS: Cabinets/CDER_OC/OSI/OSIS--Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL SITES/ HEXAL AG, Oberhaching, Germany/BLA 761071_GP2017 proposed biosimilar to adalimumab Humira®

OSIS File #: BE 7792
FACTS: 11812299

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