CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA761105Orig1s009/010

Name: Skyrizi (risankizumab-rzaa) injection, 75 mg/0.83 mL

Sponsor: AbbVie, Inc

Approval Date: April 23, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

761105Orig1s009/10

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s009/010

APPROVAL LETTER

BLA 761105/S-009 & S-010

SUPPLEMENT APPROVAL

AbbVie Inc.
Attention: Mary Konkowski
Director, Regulatory Strategy
1 N. Waukegan Road
Dept. PA72 Bldg. AP30-4
North Chicago, IL 60064

Dear Ms. Konkowski:

Please refer to your supplemental biologics license applications (sBLA) dated and received June 26 and July 27, 2020 respectively, and your amendments, submitted under section 351(a) of the Public Health Service Act for Skyrizi (risankizumab-rzaa) injection.

This Prior Approval supplemental biologics application provides for a change to a new 150 mg/mL formulation and product presentation (pre-filled syringe with needle stick prevention) in S-009. The purpose of the supplemental BLA (sBLA) S-010 is to propose a new autoinjector product presentation using the 150 mg/mL formulation.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on March 19, 2021, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761105/S-009 and S-010**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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.

Because none of these criteria apply to your application, you are exempt from this requirement.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

1) For your AutoInjector, you state that the user needs to be able to determine if the dose was administered successfully, and therefore designed your combination product to indicate by auditory means to the user, that the injection process is complete. However, there is no specific acceptance criteria or related after-assembly release testing for this audible feedback (click sound volume, timing, correlation with dose delivery) function of your device to ensure that the quality of this attribute as designed is effectively and reliability maintained. Your intended user may solely rely on the audible feedback to indicate end of injection; therefore either,

   a) Implement and validate component inspection criteria specific to those design dimensions which are critical to maintain that the "hammers" of the control unit disengage at the stated fixed nominal distance relative to the end of the syringe barrel in order to achieve no more than (b) (4) mL at the time of the audible click. In addition, implement and validate component inspection criteria for those design dimensions which are responsible for the audible click volume.

Or

   b) Implement and provide verification testing of design input requirements and assembly release testing for your audible click volume (i.e., decibels) and timing (+/- seconds from end of injection) or residual volume after click (delivered volume remaining in device after audible click.

The timetable you submitted on April 21, 2021, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2021

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication,

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Craig Johnson, Regulatory Project Manager, at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- Carton and Container Labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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/

SHARI L TARGUM
04/26/2021 05:34:15 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s009/010

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SKYRIZI safely and effectively. See full prescribing information for SKYRIZI.

SKYRIZI® (risankizumab-rzaa) injection, for subcutaneous use
Initial U.S. Approval: 2019

RECENT MAJOR CHANGES

Dosage and Administration (2)	04/2021
Warnings and Precautions (5.3)	04/2021

INDICATIONS AND USAGE

SKYRIZI is an interleukin-23 antagonist indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. (1)

DOSAGE AND ADMINISTRATION

- 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. (2.2)

DOSAGE FORMS AND STRENGTHS

- Injection: 150 mg/mL in each single-dose prefilled pen. (3)
- Injection: 150 mg/mL in each single-dose prefilled syringe. (3)
- Injection: 75 mg/0.83 mL in each single-dose prefilled syringe. (3)

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Infections: SKYRIZI may increase the risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If such an infection develops, do not administer SKYRIZI until the infection resolves. (5.1)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment with SKYRIZI. (5.2)
- Administration of Vaccines: Avoid use of live vaccines. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 1%) are upper respiratory infections, headache, fatigue, injection site reactions, and tinea infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**.**

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SKYRIZI® is indicated for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Procedures Prior to Treatment Initiation

- Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI *[see Warnings and Precautions (5.2)]*.
- Complete all age-appropriate vaccinations as recommended by current immunization guidelines *[see Warnings and Precautions (5.3)]*.

2.2 Dosage

The recommended dosage is 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

2.3 Preparation Instructions

- Before injecting, remove the carton with SKYRIZI from the refrigerator and without removing the prefilled pen or prefilled syringe(s) from the carton, allow SKYRIZI to reach room temperature out of direct sunlight (30 to 90 minutes for the prefilled pen and 15 to 30 minutes for the prefilled syringe(s)).
- Visually inspect SKYRIZI for particulate matter and discoloration prior to administration.

  SKYRIZI 150 mg/mL is a colorless to yellow and clear to slightly opalescent solution. SKYRIZI 75 mg/0.83 mL is a colorless to slightly yellow and clear to slightly opalescent solution.

  The solution may contain a few translucent to white particles. Do not use if the solution contains large particles or is cloudy or discolored.

2.4 Administration Instructions

- SKYRIZI is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject SKYRIZI after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of SKYRIZI according to the "Instructions for Use" *[see Instructions for Use]*.

- Administer SKYRIZI subcutaneously. Do not inject into areas where the skin is tender, bruised, erythematous, indurated or affected by psoriasis. Administration of SKYRIZI in the upper, outer arm may only be performed by a healthcare professional or caregiver.
- When using SKYRIZI 150 mg/mL prefilled pen or prefilled syringe, inject one 150 mg single-dose prefilled pen or prefilled syringe.
- When using SKYRIZI 75 mg/0.83 mL prefilled syringes, for a 150 mg dose, two 75 mg prefilled syringes are required. Inject one prefilled syringe after the other in different anatomic locations (such as thighs or abdomen).
- Discard prefilled pen or prefilled syringe(s) after use. Do not reuse.

3 DOSAGE FORMS AND STRENGTHS

SKYRIZI Pen

Injection: 150 mg/mL as a colorless to yellow and clear to slightly opalescent solution in each single-dose prefilled pen.

SKYRIZI Prefilled Syringe

Injection: 150 mg/mL as a colorless to yellow and clear to slightly opalescent solution in each single-dose prefilled syringe.

Injection: 75 mg/0.83 mL as a colorless to slightly yellow and clear to slightly opalescent solution in each single-dose prefilled syringe.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections

SKYRIZI may increase the risk of infections. In clinical studies, infections occurred in 22.1% of the SKYRIZI group compared to 14.7% of the placebo group through 16 weeks of treatment. Upper respiratory tract infections and tinea infections occurred more frequently in the SKYRIZI group than in the placebo group. Subjects with known chronic or acute infections were not enrolled in clinical studies *[see Adverse Reactions (6.1)]*.

The rate of serious infections for the SKYRIZI group and the placebo group was ≤ 0.4%. Treatment with SKYRIZI should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SKYRIZI. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If a patient develops such an infection or is not

responding to standard therapy, monitor the patient closely and do not administer SKYRIZI until the infection resolves.

5.2 Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SKYRIZI. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with SKYRIZI and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks on SKYRIZI. Two subjects taking isoniazid for treatment of latent TB discontinued treatment due to liver injury. Of the 31 subjects from the IMMHANCE study with latent TB who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 55 weeks on SKYRIZI. Consider anti-TB therapy prior to initiating SKYRIZI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients for signs and symptoms of active TB during and after SKYRIZI treatment. Do not administer SKYRIZI to patients with active TB.

5.3 Administration of Vaccines

Avoid use of live vaccines in patients treated with SKYRIZI. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Prior to initiating therapy with SKYRIZI, complete all age-appropriate vaccinations according to current immunization guidelines. No data are available on the response to live or inactive vaccines.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Infections *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse drug reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 2234 subjects were treated with SKYRIZI in clinical development trials in plaque psoriasis. Of these, 1208 subjects with psoriasis were exposed to SKYRIZI for at least one year.

Data from placebo- and active-controlled trials were pooled to evaluate the safety of SKYRIZI for up to 16 weeks. In total, 1306 subjects were evaluated in the SKYRIZI 150 mg group.

Table 1 summarizes the adverse drug reactions that occurred at a rate of at least 1% and at a higher rate in the SKYRIZI group than the placebo group during the 16-week controlled period of pooled clinical trials.

Table 1. Adverse Drug Reactions Occurring in ≥ 1% of Subjects on SKYRIZI through Week 16

Adverse Drug Reactions	SKYRIZI N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	15 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection, onychomycosis

Adverse drug reactions that occurred in < 1% but > 0.1% of subjects in the SKYRIZI group and at a higher rate than in the placebo group through Week 16 were folliculitis and urticaria.

Specific Adverse Drug Reactions

Infections

In the first 16 weeks, infections occurred in 22.1% of the SKYRIZI group (90.8 events per 100 subject-years) compared to 14.7% of the placebo group (56.5 events per 100 subject-years) and did not lead to discontinuation of SKYRIZI. The rates of serious infections for the SKYRIZI group and the placebo group were ≤0.4%. Serious infections in the SKYRIZI group included cellulitis, osteomyelitis, sepsis, and herpes zoster. In ULTIMMA-1 and ULTIMMA-2, through Week 52, the rate of infections (73.9 events per 100 subject-years) was similar to the rate observed during the first 16 weeks of treatment.

Safety Through Week 52

Through Week 52, no new adverse reactions were identified, and the rates of the adverse reactions were similar to those observed during the first 16 weeks of treatment. During this period, serious infections that led to study discontinuation included pneumonia.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products, including other risankizumab products, may be misleading.

By Week 52, approximately 24% (263/1079) of subjects treated with SKYRIZI at the recommended dose developed antibodies to risankizumab-rzaa. Of the subjects who developed antibodies to risankizumab-rzaa, approximately 57% (14% of all subjects treated with SKYRIZI) had antibodies that were classified as neutralizing. Higher antibody titers in approximately 1% of subjects treated with SKYRIZI were associated with lower risankizumab-rzaa concentrations and reduced clinical response.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women with plaque psoriasis who become pregnant while treated with SKYRIZI. Patients should be encouraged to enroll by calling 1-877-302-2161.

Risk Summary

Limited available data with SKYRIZI use in pregnant women are insufficient to evaluate a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Human IgG is known to cross the placental barrier; therefore, SKYRIZI may be transmitted from the mother to the developing fetus.

In an enhanced pre- and post-natal developmental toxicity study, pregnant cynomolgus monkeys were administered subcutaneous doses of 5 and 50 mg/kg risankizumab-rzaa once weekly during the period of organogenesis up to parturition. At the 50 mg/kg dose [20 times the maximum recommended human dose (MRHD); 2.5 mg/kg based on administration of a 150 mg dose to a 60 kg individual], increased fetal/infant loss was noted in pregnant monkeys *(see Data)*. No risankizumab-rzaa-related effects on functional or immunological development were observed in infant monkeys from birth through 6 months of age. The clinical significance of these findings for humans is unknown.

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

Data

Animal Data

An enhanced pre- and post-natal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered weekly subcutaneous doses of risankizumab-rzaa of 5 or 50 mg/kg from gestation day 20 to parturition and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology or neurobehavioral development. However, a dose-dependent increase in fetal/infant loss was noted in the risankizumab-rzaa-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared to the vehicle

control group (19%). The increased fetal/infant loss in the 50 mg/kg group was considered to be related to risankizumab-rzaa treatment. The no observed adverse effect level (NOAEL) for maternal toxicity was identified as 50 mg/kg (20 times the MRHD, based on mg/kg comparison) and the NOAEL for developmental toxicity was identified as 5 mg/kg (2 times the MRHD, based on mg/kg comparison). In the infants, mean serum concentrations increased in a dose-dependent manner and were approximately 17-86% of the respective maternal concentrations. Following delivery, most adult female cynomolgus monkeys and all infants from the risankizumab-rzaa-treated groups had measurable serum concentrations of risankizumab-rzaa up to 91 days postpartum. Serum concentrations were below detectable levels at 180 days postpartum.

8.2 Lactation

Risk Summary

There are no data on the presence of risankizumab-rzaa in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SKYRIZI and any potential adverse effects on the breastfed infant from SKYRIZI or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of SKYRIZI in pediatric patients less than 18 years of age have not yet been established.

8.5 Geriatric Use

Of the 2234 subjects with plaque psoriasis exposed to SKYRIZI, 243 subjects were 65 years or older and 24 subjects were 75 years or older. No overall differences in risankizumab-rzaa exposure, safety or effectiveness were observed between older and younger subjects who received SKYRIZI. However, the number of subjects aged 65 years and older was not sufficient to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and administer appropriate symptomatic treatment immediately.

11 DESCRIPTION

Risankizumab-rzaa, an interleukin-23 antagonist, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody. Risankizumab-rzaa is produced by recombinant DNA technology in Chinese hamster ovary cells and has an approximate molecular weight of 149 kDa.

SKYRIZI 150 mg/mL prefilled syringe and prefilled pen

SKYRIZI (risankizumab-rzaa) injection is a sterile, preservative-free, colorless to yellow, and clear to slightly opalescent solution for subcutaneous use.

Each SKYRIZI 150 mg/mL prefilled pen and prefilled syringe contains acetic acid (0.054 mg), polysorbate 20 (0.2 mg), sodium acetate trihydrate (1.24 mg), trehalose dihydrate (70 mg), and Water for Injection, USP. The pH is 5.7.

SKYRIZI 75 mg/0.83 mL prefilled syringe

SKYRIZI (risankizumab-rzaa) injection is a sterile, preservative-free, colorless to slightly yellow, and clear to slightly opalescent solution for subcutaneous use.

Each SKYRIZI 75 mg/0.83 mL prefilled syringe contains disodium succinate hexahydrate (0.88 mg), polysorbate 20 (0.17 mg), sorbitol (34 mg), succinic acid (0.049 mg), and Water for Injection, USP. The pH is 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Risankizumab-rzaa is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses.

Risankizumab-rzaa inhibits the release of pro-inflammatory cytokines and chemokines.

12.2 Pharmacodynamics

No formal pharmacodynamics studies have been conducted with risankizumab-rzaa.

12.3 Pharmacokinetics

Risankizumab-rzaa plasma concentrations increased dose-proportionally from 90 to 180 mg and from 18 to 300 mg (0.6 to 1.2 and 0.12 to 2.0 times the approved recommended dosage) following subcutaneous administration in subjects with plaque psoriasis and healthy volunteers, respectively. Steady-state concentrations were achieved by Week 16 following subcutaneous administration of risankizumab-rzaa at Weeks 0, 4, and every 12 weeks thereafter. At the 150 mg dose, the estimated steady-state peak concentration (C_{max}) and trough concentration (C_{trough}) were approximately 12 mcg/mL and 2 mcg/mL, respectively.

Absorption

The absolute bioavailability of risankizumab-rzaa was estimated to be 89% following subcutaneous injection. C_{max} was reached by 3-14 days.

Distribution

The estimated steady-state volume of distribution (inter-subject CV%) was 11.2 L (34%) in subjects with plaque psoriasis.

Elimination

The estimated systemic clearance (inter-subject CV%) was 0.31 L/day (24%) and terminal elimination half-life was approximately 28 days in subjects with plaque psoriasis.

Metabolism

The metabolic pathway of risankizumab-rzaa has not been characterized. As a humanized IgG1 monoclonal antibody, risankizumab-rzaa is expected to be degraded into small peptides and amino acids via catabolic pathways in a manner similar to endogenous IgG.

Specific Populations

No clinically significant differences in the pharmacokinetics of risankizumab-rzaa were observed based on age (≥18 years). No specific studies have been conducted to determine the effect of renal or hepatic impairment on the pharmacokinetics of risankizumab-rzaa.

Body Weight

Risankizumab-rzaa clearance and volume of distribution increase and plasma concentrations decrease as body weight increases; however, no dose adjustment is recommended based on body weight.

Drug Interaction Studies

Cytochrome P450 Substrates

No clinically significant changes in exposure of caffeine (CYP1A2 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate), or midazolam (CYP3A substrate) were observed when used concomitantly with risankizumab-rzaa 150 mg administered subcutaneously at Weeks 0, 4, 8 and 12 (more frequent than the approved recommended dosing frequency) in subjects with plaque psoriasis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with SKYRIZI.

No effects on male fertility parameters were observed in sexually mature male cynomolgus monkeys subcutaneously treated with 50 mg/kg risankizumab-rzaa (at 20 times the clinical exposure at the MRHD, based on mg/kg comparison) once weekly for 26 weeks.

14 CLINICAL STUDIES

Four multicenter, randomized, double-blind studies [ULTIMMA-1 (NCT02684370), ULTIMMA-2 (NCT02684357), IMMHANCE (NCT02672852), and IMMVENT (NCT02694523)] enrolled 2109 subjects 18 years of age and older with moderate to severe plaque psoriasis who had a body surface area (BSA) involvement of ≥10%, a static Physician's Global Assessment (sPGA) score of ≥3 ("moderate") in the overall assessment (plaque thickness/induration, erythema, and scaling) of psoriasis on a severity scale of 0 to 4, and a Psoriasis Area and Severity Index (PASI) score ≥12.

Overall, subjects had a median baseline PASI score of 17.8 and a median BSA of 20.0%. Baseline sPGA score was 4 ("severe") in 19% of subjects. A total of 10% of study subjects had a history of diagnosed psoriatic arthritis.

Across all studies, 38% of subjects had received prior phototherapy, 48% had received prior non-biologic systemic therapy, and 42% had received prior biologic therapy for the treatment of psoriasis.

ULTIMMA-1 and ULTIMMA-2

In ULTIMMA-1 and ULTIMMA-2, 997 subjects were enrolled (including 598 subjects randomized to the SKYRIZI 150 mg group, 200 subjects randomized to the placebo group, and 199 to the biologic active control group). Subjects received treatment at Weeks 0, 4, and every 12 weeks thereafter.

Both studies assessed the responses at Week 16 compared to placebo for the two co-primary endpoints:

- the proportion of subjects who achieved an sPGA score of 0 ("clear") or 1 ("almost clear")
- the proportion of subjects who achieved at least a 90% reduction from baseline PASI (PASI 90)

Secondary endpoints included the proportion of subjects who achieved PASI 100, sPGA 0, and PSS 0 at Week 16.

The results are presented in Table 2.

Table 2. Efficacy Results at Week 16 in Adults with Plaque Psoriasis in ULTIMMA-1 and ULTIMMA-2

	ULTIMMA-1		**ULTIMMA-2**	
	SKYRIZI (N=304) n (%)	**Placebo (N=102) n (%)**	**SKYRIZI (N=294) n (%)**	**Placebo (N=98) n (%)**
sPGA 0 or 1 ("clear or almost clear")[a]	267 (88)	8 (8)	246 (84)	5 (5)
PASI 90[a]	229 (75)	5 (5)	220 (75)	2 (2)
sPGA 0 ("clear")	112 (37)	2 (2)	150 (51)	3 (3)
PASI 100	109 (36)	0 (0)	149 (51)	2 (2)
[a] Co-primary endpoints				

Examination of age, gender, race, body weight, baseline PASI score and previous treatment with systemic or biologic agents did not identify differences in response to SKYRIZI among these subgroups at Week 16.

In ULTIMMA-1 and ULTIMMA-2 at Week 52, subjects receiving SKYRIZI achieved sPGA 0 (58% and 60%, respectively), PASI 90 (82% and 81%, respectively), and PASI 100 (56% and 60%, respectively).

Patient Reported Outcomes

Improvements in signs and symptoms related to pain, redness, itching and burning at Week 16 compared to placebo were observed in both studies as assessed by the Psoriasis Symptom Scale (PSS). In ULTIMMA-1 and ULTIMMA-2, about 30% of the subjects who received SKYRIZI achieved PSS 0 ("none") at Week 16 compared to 1% of the subjects who received placebo.

IMMHANCE

IMMHANCE enrolled 507 subjects (407 randomized to SKYRIZI 150 mg and 100 to placebo). Subjects received treatment at Weeks 0, 4, and every 12 weeks thereafter.

At Week 16, SKYRIZI was superior to placebo on the co-primary endpoints of sPGA 0 or 1 (84% SKYRIZI and 7% placebo) and PASI 90 (73% SKYRIZI and 2% placebo). The respective response rates for SKYRIZI and placebo at Week 16 were: sPGA 0 (46% SKYRIZI and 1% placebo); PASI 100 (47% SKYRIZI and 1% placebo); and PASI 75 (89% SKYRIZI and 8% placebo).

Maintenance and Durability of Response

In ULTIMMA-1 and ULTIMMA-2, among the subjects who received SKYRIZI and had PASI 100 at Week 16, 80% (206/258) of the subjects who continued on SKYRIZI had PASI 100 at Week 52. For PASI 90 responders at Week 16, 88% (398/450) of the subjects had PASI 90 at Week 52.

In IMMHANCE, subjects who were originally on SKYRIZI and had sPGA 0 or 1 at Week 28 were re-randomized to continue SKYRIZI every 12 weeks or withdrawal of therapy. At Week 52, 87% (97/111) of the subjects re-randomized to continue treatment with SKYRIZI had sPGA 0 or 1 compared to 61% (138/225) who were re-randomized to withdrawal of SKYRIZI.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

SKYRIZI (risankizumab-rzaa) injection is supplied in the following strengths:

Strength	**Pack Size**	**NDC**
150 mg/mL single-dose pen	Carton of 1	0074-2100-01
150 mg/mL single-dose prefilled syringe	Carton of 1	0074-1050-01
75 mg/0.83 mL single-dose prefilled syringe	Carton of 2	0074-2042-02

SKYRIZI (risankizumab-rzaa) injection 150 mg/mL prefilled syringe and prefilled pen contain a sterile, preservative-free, colorless to yellow, and clear to slightly opalescent solution. Each single-dose prefilled syringe or prefilled pen consists of a 1 mL glass syringe with a fixed 27-gauge ½ inch needle with needle guard.

SKYRIZI (risankizumab-rzaa) injection 75 mg/0.83 mL prefilled syringe contains a sterile, preservative-free, colorless to slightly yellow and clear to slightly opalescent solution. Each single-dose prefilled syringe consists of a 1 mL glass syringe with a fixed 29-gauge ½ inch needle with needle guard.

Storage and Handling

- Store in a refrigerator at 2°C to 8°C (36°F to 46° F).
- Do not freeze.
- Do not shake.
- Keep prefilled pens and prefilled syringes in the original cartons to protect from light.
- Not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Infections

Inform patients that SKYRIZI may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions (5.1)]*.

Administration of Vaccines

Advise patients that vaccination with live vaccines is not recommended during SKYRIZI treatment and immediately prior to or after SKYRIZI treatment. Medications that interact with the immune system may increase the risk of infection following administration of live vaccines. Instruct patients to inform the healthcare practitioner that they are taking SKYRIZI prior to a potential vaccination *[see Warnings and Precautions (5.3)]*.

Administration Instruction

Instruct patients or caregivers to perform the first self-injected dose under the supervision and guidance of a qualified healthcare professional for training in preparation and administration of SKYRIZI, including choosing anatomical sites for administration, and proper subcutaneous injection technique *[see* Instructions for Use].

If using SKYRIZI 75 mg/0.83 mL, instruct patients or caregivers to administer two 75 mg single-dose syringes to achieve the full 150 mg dose of SKYRIZI *[see Instructions for Use]*.

Instruct patients or caregivers in the technique of pen or syringe disposal *[see Instructions for Use]*.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women with plaque psoriasis exposed to SKYRIZI during pregnancy and patients can call 1-877-302-2161 *[see Use in Specific Populations 8.1]*.

Manufactured by:
AbbVie Inc.
North Chicago, IL 60064, USA

US License Number 1889
SKYRIZI® is a registered trademark of AbbVie Biotechnology Ltd.

20067753-R1 04/2021

Medication Guide
SKYRIZI® (sky-RIZZ-ee)
(risankizumab-rzaa)
injection, for subcutaneous use

What is the most important information I should know about SKYRIZI?
SKYRIZI may cause serious side effects, including:
Infections. SKYRIZI may lower the ability of your immune system to fight infections and may increase your risk of infections. Your healthcare provider should check you for infections and tuberculosis (TB) before starting treatment with SKYRIZI and may treat you for TB before you begin treatment with SKYRIZI if you have a history of TB or have active TB. Your healthcare provider should watch you closely for signs and symptoms of TB during and after treatment with SKYRIZI. Tell your healthcare provider right away if you have an infection or have symptoms of an infection, including:

- fever, sweats, or chills
- cough
- shortness of breath
- blood in your mucus (phlegm)
- muscle aches
- warm, red, or painful skin or sores on your body different from your psoriasis
- weight loss
- diarrhea or stomach pain
- burning when you urinate or urinating more often than normal

See **"What are the possible side effects of SKYRIZI?"** for more information about side effects.

What is SKYRIZI?
SKYRIZI is a prescription medicine used to treat adults with moderate to severe plaque psoriasis who may benefit from taking injections or pills (systemic therapy) or treatment using ultraviolet or UV light (phototherapy).
It is not known if SKYRIZI is safe and effective in children under 18 years of age.

Before using SKYRIZI, tell your healthcare provider about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section **"What is the most important information I should know about SKYRIZI?"**
- have an infection that does not go away or that keeps coming back.
- have TB or have been in close contact with someone with TB.
- have recently received or are scheduled to receive an immunization (vaccine). Medications that interact with the immune system may increase your risk of getting an infection after receiving live vaccines. You should avoid receiving live vaccines right before, during, or right after treatment with SKYRIZI. Tell your healthcare provider that you are taking SKYRIZI before receiving a vaccine.
- are pregnant or plan to become pregnant. It is not known if SKYRIZI can harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if SKYRIZI passes into your breast milk.
- If you become pregnant while taking SKYRIZI, you are encouraged to enroll in the Pregnancy Registry. The purpose of the pregnancy registry is to collect information about the health of you and your baby. Talk to your healthcare provider or call 1-877-302-2161 to enroll in this registry.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I use SKYRIZI?
See the detailed "Instructions for Use" that comes with SKYRIZI for information on how to prepare and inject a dose of SKYRIZI, and how to properly throw away (dispose of) used SKYRIZI prefilled pen or prefilled syringe.

- Use SKYRIZI exactly as your healthcare provider tells you to use it.
- If you miss your SKYRIZI dose, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. Call your healthcare provider if you are not sure what to do.
- If you inject more SKYRIZI than prescribed, call your healthcare provider right away.

What are the possible side effects of SKYRIZI?
SKYRIZI may cause serious side effects. See "What is the most important information I should know about SKYRIZI?"
The most common side effects of SKYRIZI include:

- upper respiratory infections
- headache
- feeling tired
- injection site reactions
- fungal skin infections

These are not all of the possible side effects of SKYRIZI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SKYRIZI?

- Store SKYRIZI in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Do not freeze SKYRIZI.
- Do not shake SKYRIZI.
- Keep SKYRIZI in the original carton to protect it from light.
- SKYRIZI is not made with natural rubber latex.

Keep SKYRIZI and all medicines out of the reach of children.

General information about the safe and effective use of SKYRIZI

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use SKYRIZI for a condition for which it was not prescribed. Do not give SKYRIZI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SKYRIZI that is written for health professionals.

What are the ingredients in SKYRIZI?

Active ingredient: risankizumab-rzaa

SKYRIZI 150 mg/mL inactive ingredients: acetic acid, polysorbate 20, sodium acetate trihydrate, trehalose dihydrate, and Water for Injection, USP.

SKYRIZI 75 mg/0.83 mL inactive ingredients: disodium succinate hexahydrate, polysorbate 20, sorbitol, succinic acid, and Water for Injection, USP.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

For more information, call 1-866-SKYRIZI (1-866-759-7494) or go to www.SKYRIZI.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 04/2021
20067753-R1

INSTRUCTIONS FOR USE
SKYRIZI® (sky-RIZZ-ee) **Pen**
(risankizumab-rzaa)
injection, for subcutaneous use

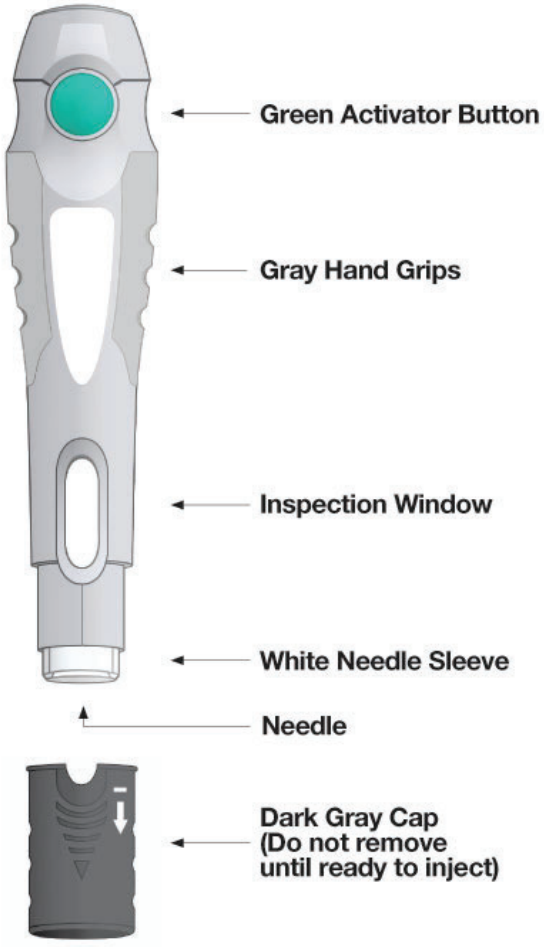
Read Before First Use

Refer to the **Medication Guide** for product information.

Read this Instructions for Use before using SKYRIZI Pen (risankizumab-rzaa) injection.

Before using SKYRIZI, you should receive training from your healthcare provider on how to inject SKYRIZI.

SKYRIZI Single-Dose Pen



Important Information

- Store SKYRIZI in the **refrigerator** at 36° to 46°F (2° to 8°C).
- Keep SKYRIZI in the original carton to protect from light until you are ready to use.
- **Before injecting,** take the SKYRIZI carton out of the refrigerator. **Leave** the carton at room temperature and out of direct sunlight for **30 to 90 minutes.**

- The liquid in the inspection window should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if liquid is **cloudy** or contains **flakes** or **large particles**.
- **Do not** use SKYRIZI if **expiration date (EXP)** has passed.
- **Do not** use SKYRIZI if liquid has been **frozen,** even if it has been thawed.
- **Do not** shake SKYRIZI.
- **Do not** use if SKYRIZI Pen has been **dropped or damaged.**
- **Do not** use SKYRIZI if carton perforations are **broken. Return product to pharmacy.**
- **Do not** remove the dark gray cap until right before injection.
- SKYRIZI is not made with natural rubber latex.

Prepare SKYRIZI injection

Take the SKYRIZI carton out of the refrigerator. **Leave** the carton at room temperature and out of direct sunlight for **30 to 90 minutes** before injecting.

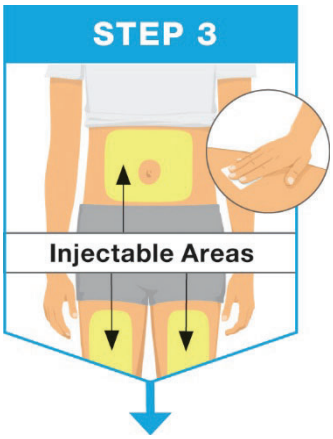
- **Do not** remove the Pen from the carton while allowing SKYRIZI to reach room temperature.
- **Do not** warm SKYRIZI in any other way. For example, **do not** warm it in a microwave or in hot water.
- **Do not** use the Pen if liquid has been frozen, even if it has been thawed.

Check expiration date **(EXP). Do not** use the Pen if expiration date has passed.

Place the following on a clean, flat surface:

- 1 single-dose SKYRIZI Pen (included)
- 1 alcohol swab (not included)
- 1 cotton ball or gauze pad (not included)
- FDA-cleared sharps disposal container (not included). See **Used SKYRIZI Prefilled Pen Disposal** for information on how to throw away (dispose of) used Pens.

Wash and dry your hands.

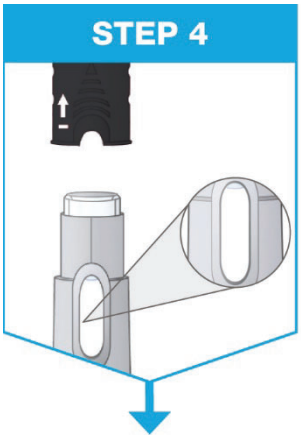


Choose an injection site:

- on the front of your **thighs** or
- your **abdomen** (belly) at least 2 inches from your navel (belly button)

Wipe the injection site in a circular motion with the alcohol swab and let it dry.

- **Do not** touch or blow on the injection site after it is cleaned. Allow the skin to dry before injecting.
- **Do not** inject through clothes.
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, has stretch marks, or areas with psoriasis.



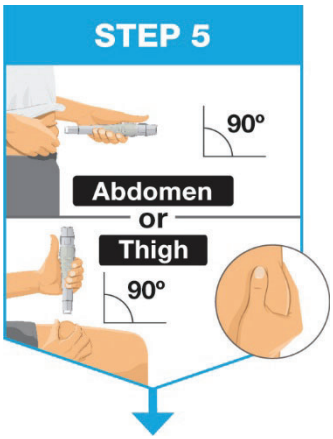
Hold the Pen with the dark gray cap pointing up.

- **Pull** the dark gray cap straight off.
- **Throw** the dark gray cap away.

Check the liquid through the inspection window.

- It is normal to see one or more bubbles in the liquid.
- The liquid should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use if the liquid is cloudy or contains flakes or large particles.

Give SKYRIZI injection

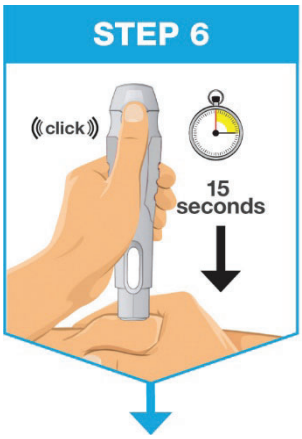


Hold the Pen with your fingers on the gray hand grips.

Turn the Pen so that the white needle sleeve points toward the injection site and you can see the green activator button.

Pinch the skin at your injection site to make a raised area and hold it firmly.

Place the white needle sleeve straight (90º angle) against the raised injection site.



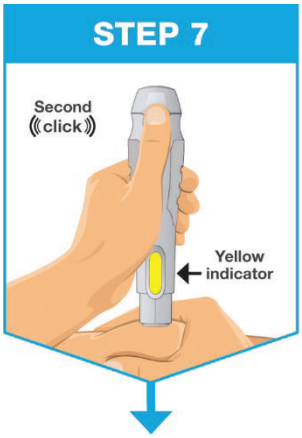
Hold the Pen so that you can see the green activator button and inspection window.

Push and keep pressing the Pen **down** against the raised injection site.

- The Pen will activate only if the white needle sleeve is pressed down against the injection site before pressing the green activator button.

Press the green activator button and hold the Pen for **15** seconds.

- The first loud “click” means the **start** of the injection.



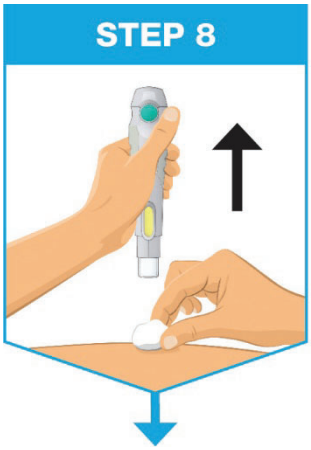
Keep pressing the Pen **down** against the injection site.

The injection is **complete** when:

- the Pen has made a second “click” **or**
- the yellow indicator has filled the inspection window

This takes **up to 15** seconds.

After SKYRIZI injection



When the injection is complete, slowly pull the Pen straight out from the skin.

The white needle sleeve will cover the needle tip and make another “click.”

After completing the injection, place a cotton ball or gauze pad on the skin at the injection site.

- **Do not** rub the injection site.
- Slight bleeding at the injection site is normal.

Throw away (dispose of) the used Pen in a FDA-cleared **sharps disposal container right away after use.**

- **Do not** dispose of used Pens in your household trash unless your community guidelines permit this.
- **Do not** recycle your sharps disposal container.

The dark gray cap, alcohol swab, cotton ball or gauze pad, and packaging may be placed in your household trash.

For more information, see Used SKYRIZI Prefilled Pen Disposal.

Important Information

- Store SKYRIZI in the **refrigerator** at 36° to 46°F (2° to 8°C).
- Keep SKYRIZI in the original carton to protect from light until you are ready to use.
- **Before injecting,** take the SKYRIZI carton out of the refrigerator. **Leave** the carton at room temperature and out of direct sunlight for **30 to 90 minutes.**
- The liquid in the inspection window should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if liquid is **cloudy** or contains **flakes** or **large particles**.
- **Do not** use SKYRIZI if **expiration date (EXP)** has passed.
- **Do not** use SKYRIZI if liquid has been **frozen,** even if it has been thawed.
- **Do not** shake SKYRIZI.
- **Do not** use if SKYRIZI Pen has been **dropped or damaged.**
- **Do not** use SKYRIZI if carton perforations are **broken. Return product to pharmacy.**
- **Do not** remove the dark gray cap until right before injection.
- SKYRIZI is not made with natural rubber latex.

Keep the SKYRIZI Pen and sharps disposal container out of the reach of children.

Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help or do not know how to proceed.

Questions About Using the SKYRIZI Pen

Q. What if I need help on how to inject SKYRIZI?
A. Call your healthcare provider **or (866) SKYRIZI or (866) 759-7494** if you need help.

Q. I have removed the dark gray cap and pressed the green activator button. Why isn't my injection starting?
A. The green activator button will not start the injection unless the white needle sleeve is pressed firmly against the injection site.

Q. How do I know when the injection is complete?
A. The injection is complete if the Pen makes a second "click" or the yellow indicator fills the inspection window. This takes up to **15** seconds.

Q. What should I do if there are more than a few drops of liquid on the injection site?
A. Call (866) SKYRIZI or (866) 759-7494 for help.

Q. What should I do with the used Pen after my injection?

A. Dispose of the used Pen in a sharps disposal container right after use. **Do not** dispose of the used Pen in your household trash.
You can sign up to receive sharps containers for SKYRIZI Pen disposal at no additional cost by going to **www.SKYRIZI.com** or calling **(866) SKYRIZI or (866) 759-7494.**

Call (866) SKYRIZI or (866) 759-7494 or go to www.SKYRIZI.com for help with your injection.

To help remember when to inject, mark your calendar with the date you give your SKYRIZI injection.

Keep the SKYRIZI Pen and sharps disposal container out of the reach of children.

Call your healthcare provider or (866) SKYRIZI or (866) 759-7494 if you need help or have questions about the use of SKYRIZI.

Used SKYRIZI Prefilled Pen Disposal

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used Pens.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal.

Do not recycle your used sharps disposal container.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

20064720-R1

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

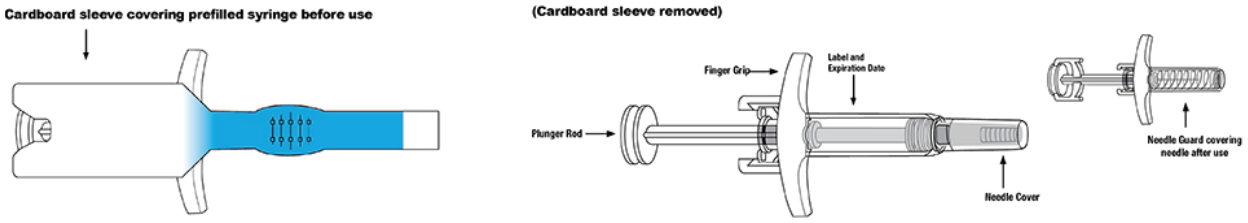
Approved: 04/2021

INSTRUCTIONS FOR USE
SKYRIZI® (sky-RIZZ-ee)
(risankizumab-rzaa)
injection, for subcutaneous use
150 mg/mL prefilled syringe

Read Before First Use

Refer to the **Medication Guide** for product information.

SKYRIZI Single-Dose Prefilled Syringe



Important Information
- Keep SKYRIZI in the original carton to protect from light until time to use.
- The liquid should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.
- **Do not** use SKYRIZI if the **expiration date (EXP:)** shown on the carton and prefilled syringe has passed.
- **Do not** use SKYRIZI if the liquid has been **frozen** (even if thawed).
- **Do not** shake SKYRIZI.
- **Do not** use SKYRIZI if the syringe has been **dropped or damaged**.
- **Do not** use SKYRIZI if carton perforations are **broken**. **Return product to the pharmacy**.
- **Do not** remove the needle cover until right before giving the injection.

Keep SKYRIZI and all medicines out of the reach of children.

Please Read Complete Instructions for Use Before Using SKYRIZI Syringe

Before Injecting
- **Receive** training on how to inject SKYRIZI before giving injection. Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help.
- **Mark your calendar** ahead of time to remember when to take SKYRIZI.
- **Leave** the carton at room temperature and out of direct sunlight for **15 to 30 minutes** to warm.
  - **Do not** remove the syringe from the carton while allowing SKYRIZI to reach room temperature.
  - **Do not** warm SKYRIZI in any other way (for example, **do not** warm it in a microwave or in hot water).

Important Information
- The liquid should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.

- **Do not** use SKYRIZI if the **expiration date (EXP:)** shown on the carton and prefilled syringe has passed.
- **Do not** use SKYRIZI if the syringe has been **dropped or damaged**.
- **Do not** use SKYRIZI if carton perforations are **broken**. **Return product to the pharmacy**.

Storage Information

- Store SKYRIZI in your refrigerator between 36° F to 46°F (2° to 8°C).
- **Do not** shake SKYRIZI.
- Keep SKYRIZI in the original carton to protect from light until time to use.
- SKYRIZI is not made with natural rubber latex.
- **Do not** use if liquid has been frozen (even if thawed).

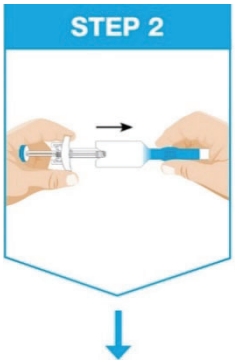
Keep SKYRIZI and all medicines out of the reach of children.

Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help or do not know how to proceed.

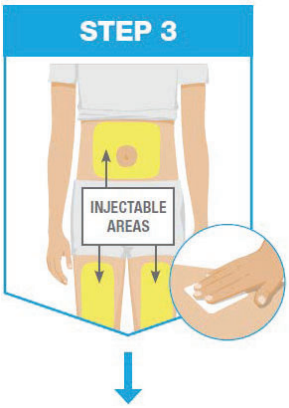
Gather the supplies for the injection.
- **Do not** hold or pull plunger rod when removing the prefilled syringe from the sleeve.

Place the following on a clean, flat surface:
- **1 prefilled syringe (included)**
- **1 alcohol swab** (not included)
- **1 cotton ball** or gauze pad (not included)
- **FDA-cleared sharps disposal container** (not included)

Wash and dry your hands.



Remove prefilled syringe from cardboard sleeve by holding the finger grip.



Pick from the 3 injectable areas:

- Front of **left thigh** or **right thigh**
- Your **abdomen** (belly) at least 2 inches from your navel (belly button)

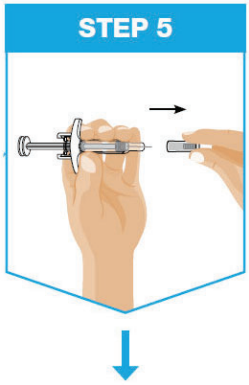
Wipe the injection site in a circular motion with the alcohol swab **before the injection.**

- **Do not** touch or blow on the injection site after it is cleaned. Allow the skin to dry before injecting.
- **Do not** inject through clothes.
- **Do not** inject into skin that is sore, bruised, red, hard, scarred, or has stretch marks, or into areas affected by psoriasis.

Hold the prefilled syringe with covered needle facing down, as shown.

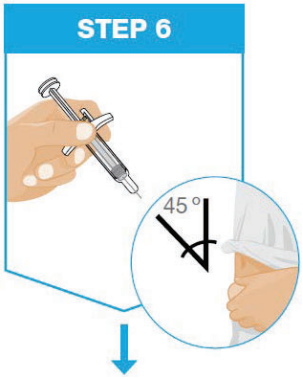
Check the liquid in the prefilled syringe.

- It is normal to see one or more bubbles in the window.
- The liquid should look clear to yellow and may contain tiny white or clear particles.
- **Do not** use the prefilled syringe if liquid is **cloudy** or contains **flakes** or **large particles**.



Remove the needle cover.

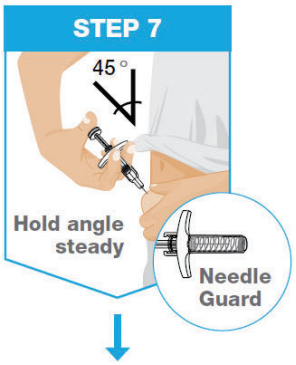
- Hold the syringe in one hand between the finger grip and needle cover.
- With the other hand, gently pull the needle cover straight off.
- **Do not** hold or pull plunger rod when removing the needle cover.
- You may see a drop of liquid at the end of the needle. This is normal.
- Throw away the needle cover.
- **Do not** touch the needle with your fingers or let the needle touch anything.



Hold the body of the prefilled syringe in one hand between the thumb and index fingers.

Pinch the area of cleaned skin with your other hand and hold it firmly.

Insert the needle into the skin at about a **45-degree angle** using a quick, short movement. Hold angle steady.



Slowly push the plunger rod all the way in until all of the liquid is injected, and the syringe is empty.
Pull the needle out of the skin while keeping the syringe at the same angle.
Release the plunger rod and allow the prefilled syringe to move up until the entire needle is covered by the needle guard.
The prefilled syringe needle guard will not activate unless all the liquid has been injected.

- **Press** a cotton ball or gauze pad over the injection site and hold for 10 seconds.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.

Put your used prefilled syringe in a **FDA-cleared sharps disposal container right away after use**.

- **Do not** throw away (dispose of) used prefilled syringe in the household trash.

For more information, see "Used SKYRIZI Prefilled Syringe Disposal" section.

Questions About Using SKYRIZI

Q. **What if I need help on how to inject SKYRIZI?**
A. Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help.

Q. **What should I do with the used prefilled syringe after my injection?**
A. Throw away (dispose of) the used prefilled syringe in a sharps disposal container and not your household trash.
You can sign up to receive sharps containers for SKYRIZI syringe disposal at no additional cost by going to **www.SKYRIZI.com** or calling **(866) SKYRIZI or (866) 759-7494**.

Q. **How do I know when the injection is complete?**
A. The injection is complete when the prefilled syringe is empty, the plunger rod is pushed all the way in, and the syringe needle guard is activated.

Used SKYRIZI Prefilled Syringe Disposal

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal.

Do not recycle your used sharps disposal container.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

20064208-R2

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

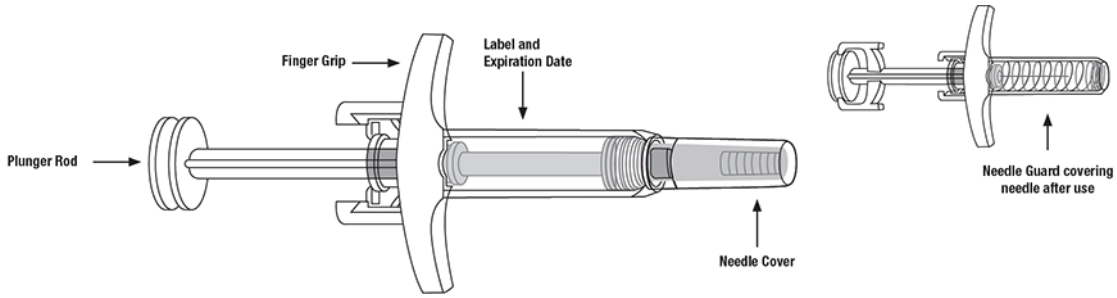
Approved: 04/2021

Instructions for Use
SKYRIZI® (sky-RIZZ-ee)
(risankizumab-rzaa)
injection, for subcutaneous use
75 mg/0.83 mL prefilled syringe

Read Before First Use

Refer to the **Medication Guide** for product information.

SKYRIZI Single-Dose Prefilled Syringe



Important Information:
- Keep SKYRIZI in the original carton to protect from light until time to use.
- The liquid should look clear to slightly yellow and may contain tiny white or clear particles.
- **DO NOT** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.
- **DO NOT** use SKYRIZI if the **expiration date (EXP:)** shown on the carton and prefilled syringe has passed.
- **DO NOT** use SKYRIZI if the liquid has been **frozen** (even if thawed).
- **DO NOT** shake SKYRIZI.
- **DO NOT** use SKYRIZI if the syringe has been **dropped or damaged**.
- **DO NOT** use SKYRIZI if carton perforations are **broken**. **Return product to the pharmacy**.
- **DO NOT** remove the needle cover until right before giving the injections.

Keep SKYRIZI and all medicines out of the reach of children.

Please Read Complete Instructions for Use Before Using SKYRIZI Syringe

Before Injecting:
- **Receive** training on how to inject SKYRIZI before giving injections. Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help.
- **Mark your calendar** ahead of time to remember when to take SKYRIZI.
- **Leave** the carton at room temperature and out of direct sunlight for **15 to 30 minutes** to warm.
  - **DO NOT** remove the syringes from the carton while allowing SKYRIZI to reach room temperature.
  - **DO NOT** warm SKYRIZI in any other way (for example, **DO NOT** warm it in a microwave or in hot water).

Important Information:
- The liquid should look clear to slightly yellow and may contain tiny white or clear particles.
- **DO NOT** use SKYRIZI if the liquid is **cloudy** or contains **flakes** or **large particles**.

- **DO NOT** use SKYRIZI if the **expiration date (EXP:)** shown on the carton and prefilled syringe has passed.
- **DO NOT** use SKYRIZI if the syringe has been **dropped or damaged**.
- **DO NOT** use SKYRIZI if carton perforations are **broken**. **Return product to the pharmacy**.

Storage Information:

- Store SKYRIZI in your refrigerator between 36° F to 46°F (2° to 8°C).
- **DO NOT** shake SKYRIZI.
- Keep SKYRIZI in the original carton to protect from light until time to use.
- SKYRIZI is not made with natural rubber latex.
- **DO NOT** use if liquid has been frozen (even if thawed).

Keep SKYRIZI and all medicines out of the reach of children.

Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help or do not know how to proceed.

Gather the supplies for the injections and place the following on a clean, flat surface:

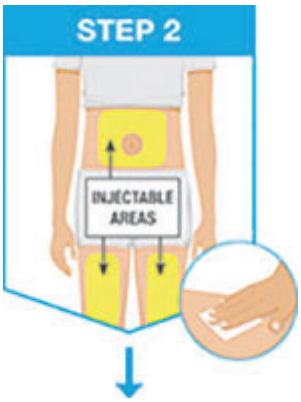
- **2 prefilled syringes** and **2 alcohol swabs (included)**
- **2 cotton balls** or gauze pads (not included)
- **FDA-cleared sharps disposal container** (not included)

Wash and dry your hands.

Start with one prefilled syringe for first injection.

1 Full Dose = +

For a full dose, 2 injections are required, one after the other.



Pick from the 3 injectable areas:

- Front of **left thigh** or **right thigh**
- Your **abdomen** (belly) at least 2 inches from your navel (belly button)

When using 2nd syringe: Pick an injection site **at least 1 inch away** from 1st site. **DO NOT inject into the same site.**

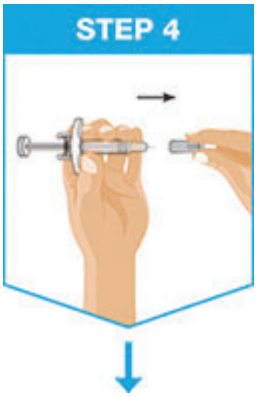
Wipe the injection site in a circular motion with the alcohol swab (before **both injections**)

- **DO NOT** touch or blow on the injection site after it is cleaned. Allow the skin to dry before injecting.
- **DO NOT** inject through clothes.
- **DO NOT** inject into skin that is sore, bruised, red, hard, scarred, or has stretch marks, or into areas affected by psoriasis.

Hold the prefilled syringe with covered needle facing down, as shown.

Check the liquid in the prefilled syringe.

- It is normal to see one or more bubbles in the window.
- The liquid should look clear to slightly yellow and may contain tiny white or clear particles.
- **DO NOT** use the prefilled syringe if liquid is **cloudy** or contains **flakes** or **large particles**.



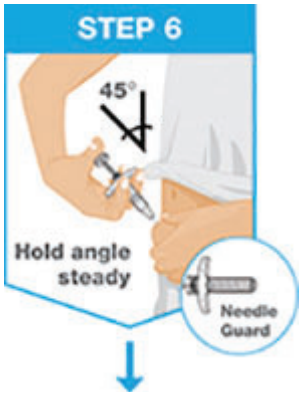
Remove the needle cover.

- Hold the syringe in one hand between the finger grip and needle cover.
- With the other hand, gently pull the needle cover straight off.
- **DO NOT** hold or pull plunger rod when removing the needle cover.
- You may see a drop of liquid at the end of the needle. This is normal.
- Throw away the needle cover.
- **DO NOT** touch the needle with your fingers or let the needle touch anything.

Hold the body of the prefilled syringe in one hand between the thumb and index fingers.

Gently pinch the area of cleaned skin with your other hand and hold it firmly.

Insert the needle into the skin at about a **45-degree angle** using a quick, short movement. Hold angle steady.



Slowly push the plunger rod all the way in until all of the liquid is injected, and the syringe is empty.

Pull the needle out of the skin while keeping the syringe at the same angle.

Release the plunger rod and allow the prefilled syringe to move up until the entire needle is covered by the needle guard.

The prefilled syringe needle guard will not activate unless all the liquid has been injected.

- **Press** a cotton ball or gauze pad over the injection site and hold for 10 seconds.
- **DO NOT** rub the injection site. You may have slight bleeding. This is normal.

Repeat Steps 2 through 6 with the 2nd prefilled syringe for a **full dose**.

- Use the 2nd prefilled syringe right after using the 1st syringe.

Put your used prefilled syringes in a **FDA-cleared sharps disposal container right away after use**.

- **DO NOT** throw away (dispose of) used prefilled syringes in the household trash.

For more information, see "Used SKYRIZI Prefilled Syringe Disposal" section.

Questions About Using SKYRIZI

Q. **What if I need help on how to inject SKYRIZI?**
A. Call your healthcare provider or **(866) SKYRIZI or (866) 759-7494** if you need help.

Q. **What should I do with both used prefilled syringes after my injections?**
A. Throw away (dispose of) both used prefilled syringes in a sharps disposal container and not your household trash.
You can sign up to receive sharps containers for SKYRIZI syringe disposal at no additional cost by going to **www.SKYRIZI.com** or calling **(866) SKYRIZI or (866) 759-7494**.

Q. **How do I know when the injection is complete?**
A. The injection is complete when the prefilled syringe is empty, the plunger rod is pushed all the way in, and the syringe needle guard is activated.

Used SKYRIZI Prefilled Syringe Disposal

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: www.fda.gov/safesharpsdisposal.

Do not recycle your used sharps disposal container.

Manufactured by: AbbVie Inc., North Chicago, IL 60064, U.S.A.
US License Number 1889

03C648

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 04/2021

Lift Tab to Open

Discard prefilled pen after use. Do not reuse.
See package insert for full prescribing information.
Do not use beyond the expiration date.

DO NOT SHAKE.
DO NOT FREEZE.
Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).
Store pen in carton until time of administration to protect from light.

Return to physician if carton perforations are broken.

Rx only
abbvie

TO OPEN

ATTENTION PHYSICIAN:
Each patient is required to receive the enclosed Medication Guide.
The entire carton is to be dispensed as a unit.
Return to physician if carton perforations are broken.

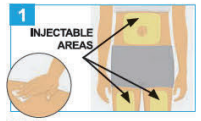
NDC 0074-2100-70
NOT FOR SALE

One 1 mL Single-Dose Prefilled Pen

Skyrizi® PEN 150 mg/mL
risankizumab-rzaa
Injection

FOR SUBCUTANEOUS USE ONLY

www.SKYRIZI.com



PICK
- **Wash** and dry your hands.
- **Pick** belly or thigh for an injection site.
- **Wipe** clean with an alcohol swab.

PULL
- **Pull** Cap off.
- **Throw** the cap away.

PLACE
- **Pinch** skin together at injection site to create raised area.
- **Place** end of Pen onto raised area of skin at a **90° angle** so you can see the window.

PUSH & HOLD
- **Press** Pen firmly against skin.
- **Push** button and hold Pen for **15 seconds.**
- **Hold** Pen firmly until the Pen has made a second "click" or the yellow indicator has filled the window.

Each 1-mL Sterile Single-Dose Pen Contains:

Risankizumab-rzaa	150 mg
Acetic acid, glacial	0.054 mg
Polysorbate 20	0.2 mg
Sodium acetate trihydrate	1.24 mg
Trehalose dihydrate	70 mg

Water for Injection, USP

Contains no preservatives. No U.S. standard of potency.

NOT FOR SALE

This carton contains:
- 1 single-dose prefilled Pen
- 1 package insert with Medication Guide
- 1 Instructions for Use

Manufactured by:
AbbVie Inc.
North Chicago, IL 60064, USA

20064352 R1

U.S. License No. 1889
Product of Germany

NDC 0074-2100-70
NOT FOR SALE

One 1 mL Single-Dose Prefilled Pen

Skyrizi® PEN 150 mg/mL
risankizumab-rzaa
Injection

FOR SUBCUTANEOUS USE ONLY

www.SKYRIZI.com

Rx only
abbvie

Lot:/EXP:

Human readable formats:
[imprint two lines]
XXXXXXX
MMMYYYY

Reference ID: 4785686

Reference ID: 4785686

Front of Paperboard Insert

Reference ID: 4785686

Back of Paperboard Insert

Reference ID: 4785686

Lift Tab to Open

Discard prefilled pen after use. Do not reuse.
See package insert for full Prescribing Information.
Do not use beyond the expiration date.

Store pen in carton until time of administration to protect from light.
Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).
DO NOT FREEZE.
DO NOT SHAKE.

www.SKYRIZI.com

One 1 mL Single-Dose Prefilled Pen

Skyrizi® PEN 150 mg/mL
risankizumab-rzaa
Injection

FOR SUBCUTANEOUS USE ONLY

▲ TO OPEN

abbvie

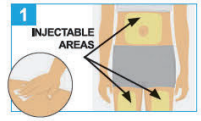
Rx only

The entire carton is to be dispensed as a unit.

ATTENTION PHARMACIST:
Each patient is required to receive the enclosed Medication Guide.

Return to pharmacy if carton perforations are broken

NDC 0074-2100-01



PICK
- **Wash** and dry your hands.
- **Pick** belly or thigh for an injection site.
- **Wipe** clean with an alcohol swab.

PULL
- **Pull** Cap off.
- **Throw** the cap away.

PLACE
- **Pinch** skin together at injection site to create raised area.
- **Place** end of Pen onto raised area of skin at a **90° angle** so you can see the window.

PUSH & HOLD
- **Press** Pen firmly against skin.
- **Push** button and hold Pen for **15 seconds**.
- **Hold** Pen firmly until the Pen has made a second "click" or the yellow indicator has filled the window.

Each 1-mL Sterile Single-Dose Pen Contains:

Risankizumab-rzaa	150 mg
Acetic acid, glacial	0.054 mg
Polysorbate 20	0.2 mg
Sodium acetate trihydrate	1.24 mg
Trehalose dihydrate	70 mg

Water for Injection, USP

Contains no preservatives. No U.S. standard of potency.

This carton contains:
- 1 single-dose prefilled Pen
- 1 package insert with Medication Guide
- 1 Instructions for Use

Manufactured by:
AbbVie Inc.
North Chicago, IL 60064, USA

20064351 R1

U.S. License No. 1889
Product of Germany

One 1 mL Single-Dose Prefilled Pen

NDC 0074-2100-01

Skyrizi® PEN 150 mg/mL
risankizumab-rzaa
Injection

FOR SUBCUTANEOUS USE ONLY

AREA FOR PHARMACY LABEL

Rx only
abbvie

www.SKYRIZI.com

GTIN: /SN: /Lot: /EXP:

NDC 0074-2100-01
One 1 mL Single-Dose Prefilled Pen
Skyrizi® PEN 150 mg/mL
risankizumab-rzaa
Injection
FOR SUBCUTANEOUS USE ONLY
3 00742100014

Human readable formats:
[imprint four lines]
00300742100014
XXXXXXXXXXXX
XXXXXXX
MMMYYYY

2D Code data:
(01)00300742100014
(21)XXXXXXXXXXXX
(17)YYMMDD
(10)XXXXXXX

Reference ID: 4785686

Skyrizi COMPLETE

We're here for you 24/7.

If you have any questions or would like to learn about resources, including how to inject or ways to save on your SKYRIZI, call 1-866-SKYRIZI (1-866-759-7494) or go to www.SKYRIZI.com.

20064351

Reference ID: 4785686

Front of Paperboard Insert

Reference ID: 4785686

Back of Paperboard Insert

The abbreviations for Expiration Date (EXP:) and Lot Number (LOT:) will either be pre-printed in white font within the black box or post-printed in white font within the black box during the packaging process.

EXP: MMMYYYY
LOT: XXXXXXX

Lift Tab to Open

Discard prefilled syringe after use. Do not reuse.
See package insert for full Prescribing Information.
Do not use beyond the expiration date.

Store syringe in carton until time of administration to protect from light.
Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).
DO NOT FREEZE.
DO NOT SHAKE

www.SKYRIZI.com

▲ TO OPEN

Rx only
abbvie

Return to physician if carton perforations are broken

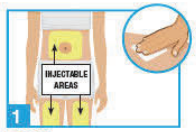
Return to physician if carton perforations are broken.
ATTENTION PHYSICIAN:
Each patient is required to receive the enclosed Medication Guide.
The entire carton is to be dispensed as a unit.

FOR SUBCUTANEOUS USE ONLY

Skyrizi® 150 mg/mL
risankizumab-rzaa
Injection

One 1 mL Single-Dose Prefilled Syringe

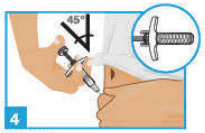
NDC 0074-1050-70
NOT FOR SALE



1 PICK
- **Wash** and dry your hands
- **Pick** thigh or belly 2 inches from navel for injection area
- **Wipe** clean the injection site

2 PREPARE
- **Pull** needle cover off the syringe
- **DO NOT** touch the needle

3 PINCH
- **Pinch** skin together at the injection site to make a raised area
- **Insert** the needle into the raised area at a 45° angle using a quick, short movement
- **Hold** angle steady



4 PUSH
- **Slowly** push the plunger in all the way until all of the medicine is injected
- **Release** the plunger and allow the needle guard to completely cover the needle

Each 1-mL Sterile Single-Dose Prefilled Syringe Contains:

Risankizumab-rzaa	150 mg
Acetic acid, glacial	0.054 mg
Polysorbate 20	0.2 mg
Sodium acetate trihydrate	1.24 mg
Trehalose dihydrate	70 mg
Water for Injection, USP	

Contains no preservatives. No U.S. standard of potency.

U.S. License No. 1889, Mfd. by: AbbVie Inc.
North Chicago, IL 60064, USA Product of Germany

This carton contains:
- 1 single-dose prefilled syringe
- 1 package insert with Medication Guide
- 1 Instructions for Use

20064210 R1

www.SKYRIZI.com

Rx only
abbvie

One 1 mL Single-Dose Prefilled Syringe

Skyrizi® 150 mg/mL
risankizumab-rzaa
Injection
FOR SUBCUTANEOUS USE ONLY

NDC 0074-1050-70
NOT FOR SALE

www.SKYRIZI.com

Rx only
abbvie

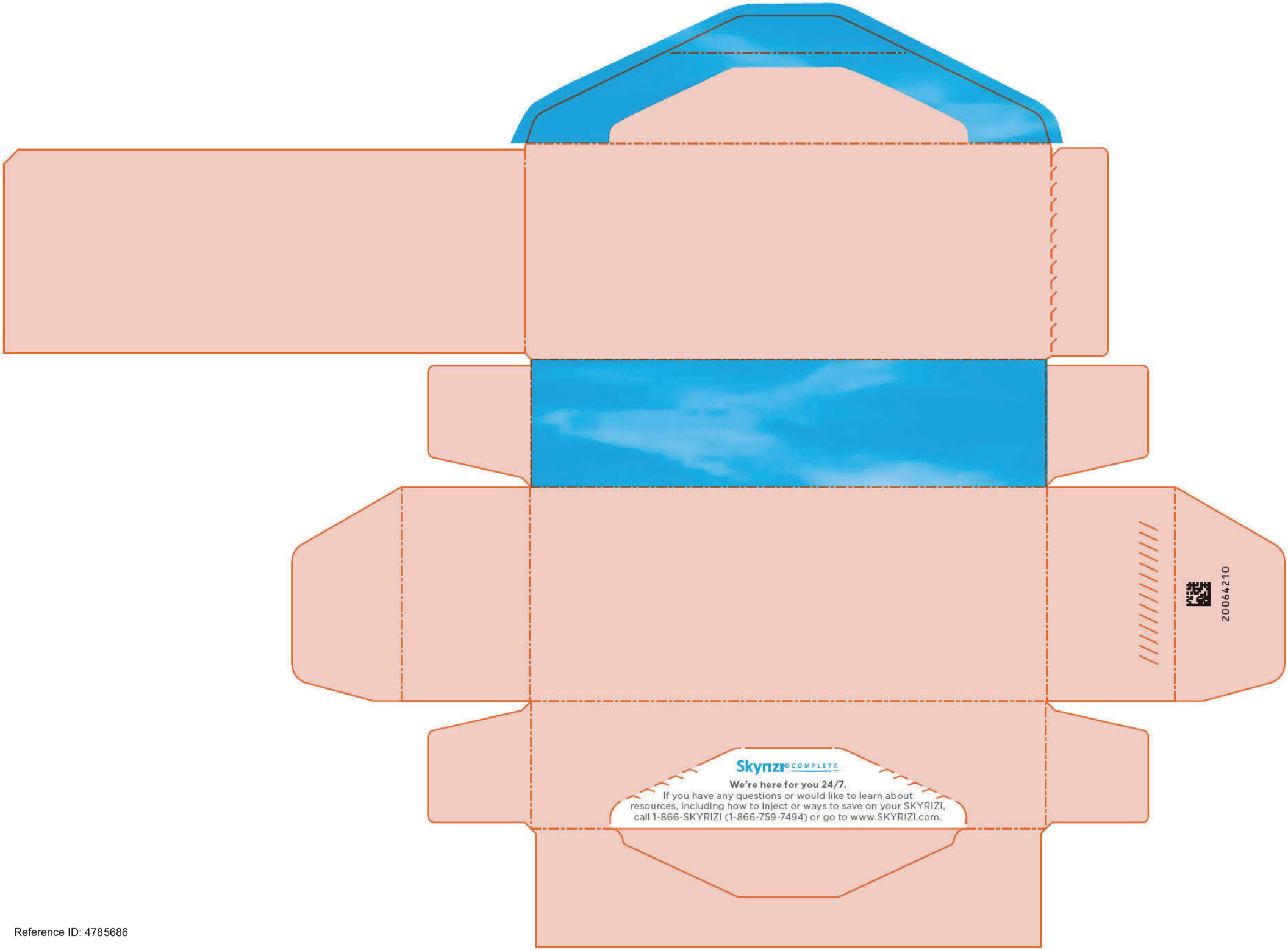
Skyrizi®
risankizumab-rzaa
Injection
FOR SUBCUTANEOUS USE ONLY

150 mg/mL

3 00741050709

One 1 mL Single-Dose Prefilled Syringe
NDC 0074-1050-70
NOT FOR SALE

Reference ID: 4785686



Reference ID: 4785686

The abbreviations for Expiration Date (EXP:), Lot Number (LOT:) and Serial Number (SN:) will either be pre-printed in white font within the black box or post-printed in white font within the black box during the packaging process.

EXP: MMMYYYY
LOT: XXXXXXXX
SN: XXXXXXXXXXXX

2D Datamatrix Encodes:
(01) 00300741050013
(21) XXXXXXXXXXXX
(17) YYMMDD
(10) XXXXXXXX

Lift Tab to Open

Discard prefilled syringe after use. Do not reuse.
See package insert for full Prescribing Information.
Do not use beyond the expiration date.

Store syringe in carton until time of administration to protect from light.
Must be refrigerated, store at 2°C to 8°C (36°F to 46°F).
DO NOT FREEZE.
DO NOT SHAKE

www.SKYRIZI.com

▲ TO OPEN

Rx only
abbvie

▶ Return to pharmacy if carton perforations are broken ◀

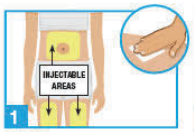
Return to pharmacy if carton perforations are broken.
ATTENTION PHARMACIST:
Each patient is required to receive the enclosed Medication Guide.
The entire carton is to be dispensed as a unit.

FOR SUBCUTANEOUS USE ONLY

Skyrizi® 150 mg/mL
risankizumab-rzaa
Injection

One 1 mL Single-Dose Prefilled Syringe

NDC 0074-1050-01



1 PICK
- **Wash** and dry your hands
- **Pick** thigh or belly 2 inches from navel for injection area
- **Wipe** clean the injection site

2 PREPARE
- **Pull** needle cover off the syringe
- **DO NOT** touch the needle

3 PINCH
- **Pinch** skin together at the injection site to make a raised area
- **Insert** the needle into the raised area at a 45° angle using a quick, short movement
- **Hold** angle steady

4 PUSH
- **Slowly** push the plunger in all the way until all of the medicine is injected
- **Release** the plunger and allow the needle guard to completely cover the needle

Each 1-mL Sterile Single-Dose Prefilled Syringe Contains:

Risankizumab-rzaa	150 mg
Acetic acid, glacial	0.054 mg
Polysorbate 20	0.2 mg
Sodium acetate trihydrate	1.24 mg
Trehalose dihydrate	70 mg
Water for Injection, USP	

Contains no preservatives. No U.S. standard of potency.

U.S. License No. 1889, Mfd. by: AbbVie Inc.
North Chicago, IL 60064, USA Product of Germany

This carton contains:
- 1 single-dose prefilled syringe
- 1 package insert with Medication Guide
- 1 Instructions for Use

20064212 R1

www.SKYRIZI.com

Rx only
abbvie

GTIN: 00300741050013

One 1 mL Single-Dose Prefilled Syringe

NDC 0074-1050-01

Skyrizi® 150 mg/mL
risankizumab-rzaa
Injection

FOR SUBCUTANEOUS USE ONLY

AREA FOR PHARMACY LABEL

Rx only
abbvie

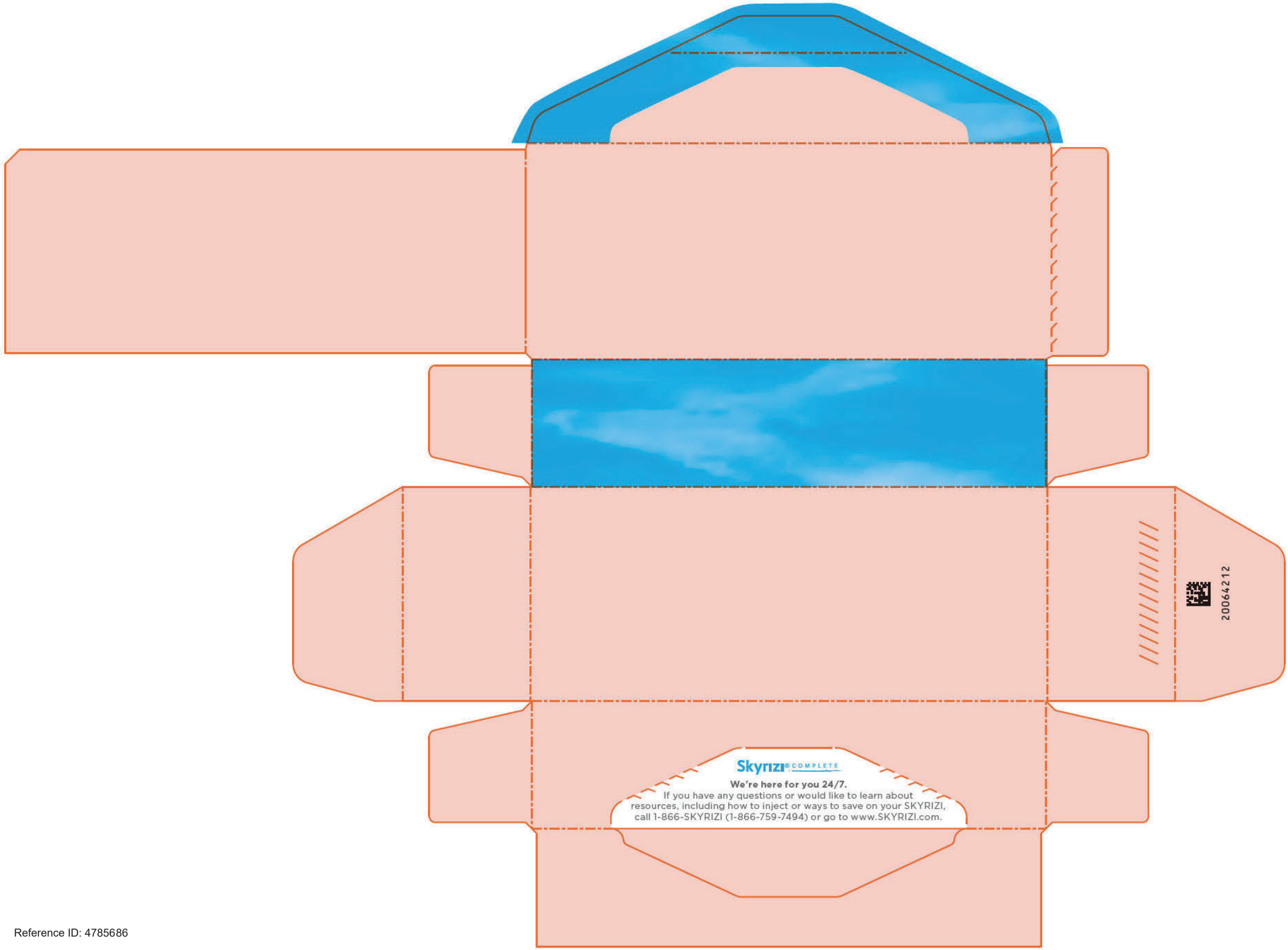
www.SKYRIZI.com

Skyrizi® 150 mg/mL
risankizumab-rzaa
Injection
FOR SUBCUTANEOUS USE ONLY

One 1 mL Single-Dose Prefilled Syringe
NDC 0074-1050-01

3 00741050013 3

Reference ID: 4785686



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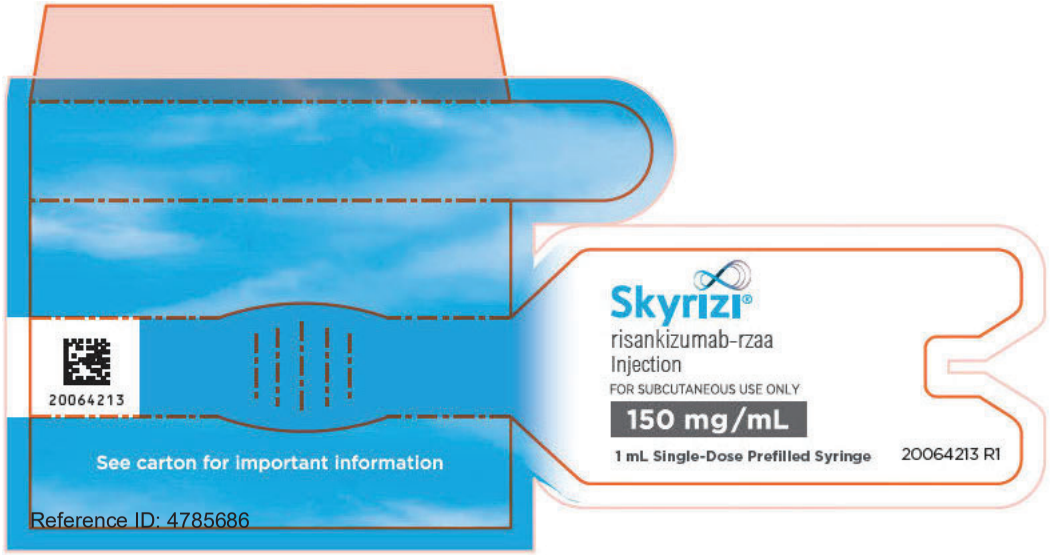

Reference ID: 4785686

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761105Orig1s009/10

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	BLA 761105/S-009 & S-010
Priority or Standard	Standard
Submit Date(s)	June 26, 2020 (S-009) July 27, 2020 (S-010)
Received Date(s)	June 26, 2020 (S-009) July 27, 2020 (S-010)
PDUFA Goal Date	April 26, 2021
Division/Office	Division of Dermatology and Dentistry /Office of Immunology and Inflammation
Review Completion Date	April 26, 2021
Established Name	risankizumab-rzaa
Trade Name	Skyrizi
Pharmacologic Class	Interleukin (IL)-23 blocker:
Code name	BI 655066
Applicant	AbbVie Inc.
Formulation(s)	PFS with needle-stick prevention device and an autoinjector (AI) or Pen
Dosing Regimen	Single dosing with the 150 mg/mL pre-filled syringe and 150 mg/ mL pen
Indication	Treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Recommendation on Regulatory Action	Approval

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Reviewers Team and Signature Approval Section

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Biostatistics Reviewer	Carin Kim, PhD	OTS/OB/DBIII	Section 7.1.2, 7.2, 7.4	**Select one:** __X__ Authored ____ Acknowledged ____ Approved
	Signature: Signature in DARRTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
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	Signature: Signature in DARRTS			

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OPDP	Laurie Buonaccorsi
PLT	Morgan Walker and Sharon Mills
OSE/DMEPA	Madhuri Patel
CDRH	Robert Nakeilny

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
PLT=Patient Labeling Team

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics

PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Skyrizi (risankizumab) injection for subcutaneous use is a humanized IgG1 monoclonal antibody that specifically binds to the p19 protein subunit of the IL-23 cytokine and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine, composed of 2 subunits (IL-23p19 and IL-12/23p40), that is involved in inflammatory and immune responses.

Skyrizi (risankizumab) was approved on April 23, 2019 as a 90 mg/mL formulation. With these supplements the sponsor provided data from their clinical development program for the 150 mg/mL subcutaneous (SC) formulation which was designed to demonstrate the bioavailability (BA), safety, and usability of the new formulation of risankizumab for the treatment of moderate to severe plaque psoriasis as was documented in the original submission for the 90 mg/mL formulation of risankizumab.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant is seeking the Agency's approval of a new formulation of 150 mg/mL administered as a single dose pre-filled syringe (PFS) or an autoinjector (AI). AI is a new device which was not approved earlier, and it will deliver the recommended 150 mg dose with a single SC injection. In sBLA 009 and 010 the following studies were submitted in support of the new formulation and device:

- Study M15-990: a PK comparability study in healthy subjects
- Study M15-999: a safety and efficacy study of the new formulation of 150 mg/mL in a PFS in subjects with psoriasis.
- Study M16-005: a usability study of the risankizumab (150 mg/mL) autoinjector combination product in subjects with psoriasis.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Supplement 9 provides for the introduction of 150mg/mL pre-filled syringe (PFS) and Supplement 10 provides for the introduction of 150mg/mL autoinjector (AI). For Skyrizi (risankizumab) injection in the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy, the dosing regimen (150 mg at weeks 0, 4 and every 12 weeks thereafter) and the route of administration (subcutaneous) will remain the same as approved for 90mg/mL PFS-NSP. The new presentations were evaluated in a Phase 1 study in healthy volunteers (bioavailability study M15-990) and two clinical studies in patients with moderate to severe plaque psoriasis (studies M15-999 and M16-005).

There are sufficient data to support the product quality of the 150 mg/ ml formulation. Bioequivalence was demonstrated between a single risankizumab-rzaa 150 mg/mL injection and two risankizumab-rzaa 75 mg/0.83 mL injections via prefilled syringe. Bioequivalence was also demonstrated between risankizumab-rzaa 150 mg/mL prefilled syringe and the prefilled pen.

The clinical trials did not identify issues related to efficacy or safety for the 150 mg/mL formulation administered by either prefilled syringe or autoinjector. Clinical trials are supportive of the demonstrated bioequivalence. Substantial efficacy and primary safety for Skyrizi (risankizumab) have been established with the 90 mg/mL formulation.

The 150 mg/mL product presentations provide patients with the benefit of a single injection instead of 2 injections to achieve each 150 mg dose.

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated, inflammatory skin disorder with a strong hereditary component. The pathogenesis of psoriasis is complex and the etiology is not completely understood. Inflammatory cytokines appear to play a role in the pathogenesis and a number of cytokines have been targeted and have demonstrated therapeutic benefit.

2.2. Analysis of Current Treatment Options

This application does not expand on treatment options. Refer to the original BLA review for comparative treatment options.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Skyrizi (risankizumab) was approved on April 23, 2019 as a 90 mg/mL formulation for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. Instructions for Use labeling was updated on March 20, 2020 to address complaints related to the usage of the PFS.

3.2. Summary of Presubmission/Submission Regulatory Activity

A Type C guidance meeting was requested to discuss the plan for supplements for the 150 mg/mL formulation in the PFS and the 150 mg/mL formulation in the AI. There were no major disagreements with the plan. The Agency agreed to the following regarding the clinical data:

- Your proposal to submit full Week 16 data and partial Week 28/Week 36 data for study M15-990 in the initial PFS submission is acceptable. The 120-day safety update should include data from the completed study (i.e. all data through Week 36). Interim analysis is not acceptable to support an action on the PFS.
- Your proposal to submit full Week 28 data and partial Week 40 data for study M15-005 in the initial AI submission is acceptable. Your proposal to submit all safety data through the Week 48 in the 120-day safety update for the AI supplement is acceptable.

The safety update report (SUR) for S009 and S010 was submitted on 10/22/2020. As advised, the applicant's SUR provides approximately 5 months of additional safety data from the final dataset for both the now completed 36-week Study M15-999 and now completed 48-week Study M16-005.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical study site inspections were not requested as the clinical studies (which includes one open-labelled study) were mainly supportive in the demonstration the comparability between the approved and new formulation.

4.2. Product Quality

Novel excipients: No
Any impurity of concern: No

OBP and OPMA reviewed the drug substance manufacturing process for the 150 mg/mL formulation and the drug product manufacturing processes for the prefilled syringe and autoinjector presentations. Refer to these reviews for additional information.

4.3. Clinical Microbiology

4.4. Devices and Companion Diagnostic Issues

CDRH conducted a review of the device constituents (prefilled syringe and autoinjector pen). Refer to Robert Nakielny's review for full details. CDRH recommends the combination product is approvable with a post marketing commitment (PMC).

The recommendation for the Post Market Commitment (6 months to a year timeframe) is to either place added Design Input Requirements around the volume level and the timing of the audible cue or to control the design criteria which these characteristics are dependent on (Critical Design Features).

5 Nonclinical Pharmacology/Toxicology

No nonclinical data was submitted for this supplement.

6 Clinical Pharmacology

6.1. Executive Summary

SKYRIZI® (risankizumab-rzaa), an interleukin-23 antagonist, was approved under BLA 761,105 in 2019 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Risankizumab is currently available as a 90 mg/mL formulation delivering a dose of 75 mg/0.83 mL prefilled syringe (PFS). The recommended dose regimen for patients with psoriasis is 150 mg which is administered by two subcutaneous (SC) injections of 75 mg/0.83 mL PFS at Week 0, Week 4, and every 12 weeks (Q12W) thereafter.
Under the current supplemental Biologics License Applications (BLA 761,105/s-009 and s-010, or sBLAs), the Applicant is seeking the Agency's approval of a new formulation of 150 mg/mL administered as a single dose PFS or an autoinjector (AI). AI is a new device which was not approved earlier, and it will deliver the recommended 150 mg dose with a single SC injection. In support of these new formulation and device submitted under sBLA 009 and 010, the following three clinical study reports are submitted.

- Study M15-990: a phase I PK comparability study in healthy subjects
- Study M15-999: a phase III safety and efficacy of the new formulation of 150 mg/mL in a PFS study in subjects with psoriasis.
- Study M16-005: a usability study of the risankizumab (150 mg/mL) autoinjector combination product in subjects with psoriasis.

6.1.1. Recommendation

From a Clinical Pharmacology perspective, the BLA 761,105/s-009 and s-010 are acceptable for approval of the new formulation of 150 mg/mL risankizumab administered as a single dose PFS or AI for the treatment of psoriasis.

6.1.2. Post-Marketing Requirements and Commitment (PMR/PMC)

None.

6.2. Summary of Clinical Trial M15-990

Title: A phase 1 study in healthy volunteers to evaluate the bioavailability of risankizumab new formulation in pre-filled syringe relative to 90 mg/mL formulation in pre-filled syringe and characterization of risankizumab pharmacokinetics using new formulation in auto-injector

Study objectives

- To assess the bioavailability of risankizumab 150 mg/mL PFS (risankizumab 150 mg/mL formulation in PFS) relative to risankizumab 90 mg/mL PFS (risankizumab 90 mg/mL formulation in PFS)
- To assess the bioavailability of risankizumab 150 mg/mL AI (risankizumab 150 mg/mL formulation in AI) relative to risankizumab 150 mg/mL PFS (risankizumab 150 mg/mL formulation in PFS)

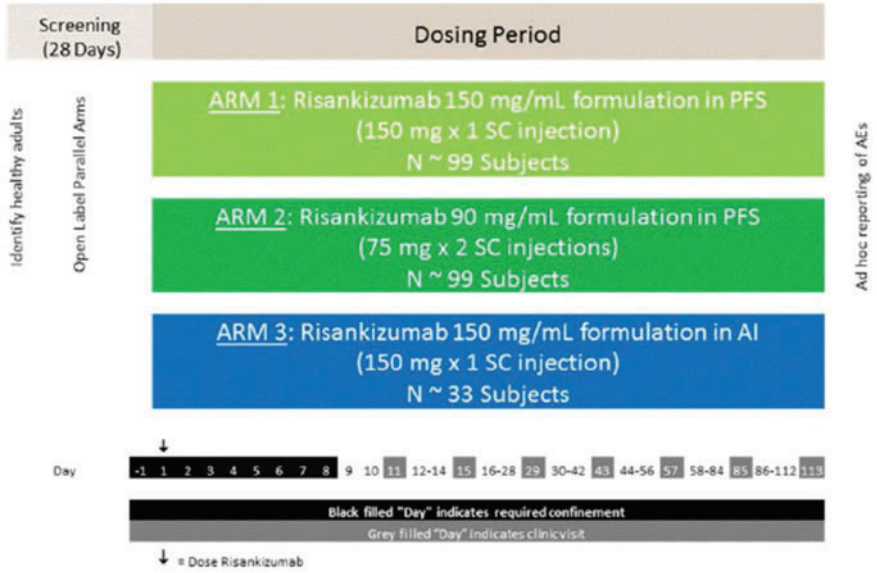
6.2.1. Study Design

This was a phase 1, single-dose, randomized, three-parallel-arm, open-label, multi-center study consisting a screening period of up to 28 days, a single dose treatment on Day 1, followed by the safety and tolerability assessment period of approximately 113 days including scheduled site visits (Figure 1).

Dosing regimen

Approximately 226 healthy adult subjects were randomized in a 3:3:1 ratio to one of the three study arms and each subject received a single SC dose of 150 mg risankizumab (Figure 1).

Figure 1 Study Design Schematic



(Source of data: Clinical Study Report M15-990, Figure 1)

Reviewer's comments: *The SC dose of 150 mg risankizumab is the recommended dose for the treatment of psoriasis in adult subjects.*

Pharmacokinetic and Immunogenicity Sampling

- Blood samples for PK assessment were collected at Baseline, on Study Days 2, 3, 4, 5, 6, 7, 8, 11, 15, 29, 43, 57, 85 and 113.
- Blood samples for immunogenicity assessment were collected at Baseline, on Study Days 15, 29, 57, 85, and 113.

6.2.2. Pharmacokinetic and Immunogenicity Results

Following a single SC administration of 150 mg risankizumab in healthy subjects,

- The risankizumab 150 mg/mL PFS was demonstrated to be bioequivalent to the currently approved risankizumab 90 mg/mL PFS with comparable PK and immunogenicity profiles (Table 1 and Table 2).
- The risankizumab 150 mg/mL AI also showed bioequivalent exposure and comparable immunogenicity profiles to the risankizumab 150 mg/mL PFS (Table 1 and Table 2).

Table 1 Risankizumab Relative Bioavailability and 90% Confidence Intervals

Arms Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Risankizumab 150 mg/mL PFS versus Risankizumab 90 mg/mL PFS	C_{max} (µg/mL)	13.0	13.3	0.974	0.902 – 1.051
	AUC_t (µg•day/mL)	512	543	0.944	0.884 – 1.007
	AUC_{inf} (µg•day/mL)	549	586	0.937	0.873 – 1.005
Risankizumab 150 mg/mL AI versus Risankizumab 150 mg/mL PFS	C_{max} (µg/mL)	13.4	13.0	1.029	0.920 – 1.150
	AUC_t (µg•day/mL)	528	512	1.031	0.938 – 1.133
	AUC_{inf} (µg•day/mL)	562	549	1.024	0.925 – 1.134

(Source of data: Clinical Study Report M15-990, Table 6)

Table 2 Incidence of ADA at Baseline and Treatment-Emergent ADA

Group	N	Baseline Incidence % (n/N)	Treatment Emergent ADA %[a] (n/N)
Arm 1	98	6.1 (6/98)	14.3 (14/98)
Arm 2	96	3.1 (3/96)	11.6 (11/95)[b]
Arm 3	32	3.1 (1/32)	9.4 (3/32)

Arm 1: risankizumab 150 mg/mL PFS
Arm 2: risankizumab 90 mg/mL PFS
Arm 3: risankizumab 150 mg/mL AI
ADA=anti-drug antibody
(Source of data: Clinical Study Report M15-990, Table 7)

6.2.3. Summary of Labeling Recommendations

Labeling recommendations are summarized as in Table 3. The text in red is proposed by the Applicant. The ~~strikethrough in red text~~ indicates recommended deletion by the reviewer. There was no new addition in section 12.3 of the labeling.

Table 3 Reviewer's Recommendations on Labeling

Proposed labeling by the Applicant	Reviewer's labeling recommendations
	(b) (4)

6.3. Question-Based Clinical Pharmacology Review

6.3.1. What are the study population in Study M15-990?

Study M15-990 enrolled 226 subjects. The demographic data is summarized in Table 4.

As body weight has been identified as a significant covariate affecting the PK of risankizumab in the original BLA, enrollment was stratified by body weight obtained upon initial confinement according to Table 5. Within each body weight group, enrolled subjects were randomized in a 3:3:1 ratio to one of the three study arms.

Table 4 Demographic Summary

Variable	Group	N	Mean	SD	Min	Max
Age (year)	Arm 1	98	37.8	10.7	18	56
	Arm 2	96	36.9	9.6	20	56
	Arm 3	32	38.4	9.9	20	55
Weight (kg)	Arm 1	98	74.2	11.8	45.1	100.5
	Arm 2	96	74.0	11.1	48.5	96.2
	Arm 3	32	73.4	11.2	49.3	96.5
Height (cm)	Arm 1	98	169.9	10.7	149.5	197.9
	Arm 2	96	170.4	9.3	147.8	190.4
	Arm 3	32	168.4	9.1	153.2	183.1
BMI (kg/m^2)	Arm 1	98	25.6	2.8	18.8	29.9
	Arm 2	96	25.4	2.6	19.6	29.9
	Arm 3	32	25.8	2.4	20.4	29.5
Sex	Arm 1	98	41 (42%) Females, 57 (58%) Males			
	Arm 2	96	42 (44%) Females, 54 (56%) Males			
	Arm 3	32	14 (44%) Females, 18 (56%) Males			
Race	Arm 1	98	61 (62%) White, 30 (31%) black, 2 (2%) Asian, 5 (5%) Multiple Race			
	Arm 2	96	47 (49%) White, 39 (41%) Black, 2 (2%) Asian, 8 (8%) Multiple Race			
	Arm 3	32	18 (56%) White, 10 (31%) Black, 1 (3%) Asian, 1 (3%) Native Hawaiian or Pacific Islander, 2 (6%) Multiple Race[a]			

SD = Standard deviation; Min = Minimum; Max = Maximum; BMI = Body Mass Index

a. Percentages do not add up to 100% due to rounding.

Arm 1: Risankizumab 150 mg/mL PFS.

Arm 2: Risankizumab 90 mg/mL PFS.

Arm 3: Risankizumab 150 mg/mL AI.

Note: All subjects were 18 - 55 years of age inclusive, upon initial confinement, age calculation is based on calendar year therefore two subjects display as 56 years old.

Cross reference: Table 14.1__2

(Source of data: Clinical Study Report M15-990, Table 4)

Table 5 Body Weight Groups

Group	Body Weight (kg)
1	< 60
2	≥ 60 to < 70
3	≥ 70 to < 80
4	≥ 80 to < 90
5	≥ 90 to < 100
6	≥ 100 to < 110

(Source of data: Clinical Study Report M15-990, Table 2)

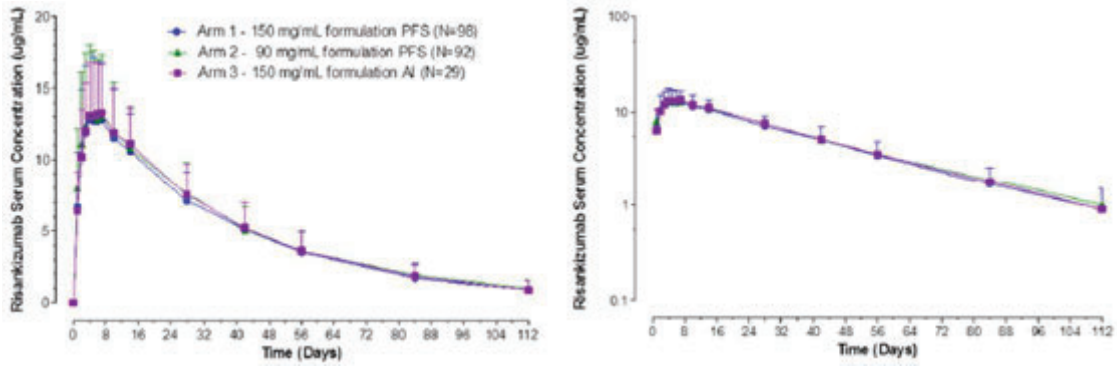
6.3.2. What are the PK results of risankizumab in Study M15-990?

Following the administration of a 150 mg SC dose either as single injection or as two injections, the risankizumab concentration-time profiles were overlapping with comparable PK parameters across all three arms (Figure 2, Table 6). The point estimates of the relative bioavailability of the risankizumab 150 mg PFS (test) compared to the risankizumab 90 mg/mL PFS (reference) based on the tested primary variables for evaluating PK comparability (Cmax, AUCt and AUCinf) ranged from 0.94 to 0.97 with the 90% confidence interval falling within the no-effect boundary of 0.80 to 1.25, demonstrating PK bioequivalence between the two formulations (Table 1). Similar results were also observed when comparing the risankizumab 150 mg/mL AI (test) to the risankizumab 150 mg/mL PFS (reference) (Table 1).

Overall, following a single SC administration of 150 mg risankizumab in healthy subjects, PK bioequivalence and comparability were demonstrated for:

- Risankizumab 150 mg/mL PFS (a new formulation) verse risankizumab 90 mg/mL PFS
- Risankizumab 150 mg/mL AI (a new device) verse risankizumab 150 mg/mL PFS

Figure 2 Risankizumab Serum Concentrations Following a Single SC Dose of 150 mg of Risankizumab



(Source of data: Clinical Study Report M15-990, Figure 2)

Table 6 Pharmacokinetics of Risankizumab Following a Single SC Does of 150 mg of Risankizumab

Pharmacokinetic Parameters	Units	Arm 1 Risankizumab 150 mg/mL PFS N = 98	Arm 2 Risankizumab 90 mg/mL PFS N = 92	Arm 3 Risankizumab 150 mg/mL AI N = 29
T_{max}[a]	days	6.0 (2.0 to 42)	5.0 (2.0 to 28)	6.0 (3.0 to 14)
C_{max}	µg/mL	13.0 (13.9, 33)	13.5 (14.2, 33)	13.7 (14.1, 25)
$t_{1/2}$[b]	days	26.6 (6.69)	27.4 (7.29)[c]	25.5 (6.23)
AUC_t	µg•day/mL	508 (535, 30)	543 (565, 28)[c]	533 (555, 29)
AUC_{inf}	µg•day/mL	544 (577, 33)	586 (613, 30)[c]	567 (594, 31)

a. Median (minimum through maximum).
b. Harmonic mean (pseudo-standard deviation).
c. N = 91 subjects, as one subject only had concentration values up to Study Day 14, and the terminal phase could not be determined.

Cross reference: Tables 14.2__3.1 through 14.2__3.3

(Source of data: Clinical Study Report M15-990, Table 5)

6.3.3. What are the immunogenicity results of risankizumab in Study M15-990 and Study M15-999?

- ***Study M15-990***

A comparison of incidence of treatment-emergent anti-drug antibodies (ADAs) is summarized in Table 7. Following administration of risankizumab 150 mg SC, 14% and 12% of healthy subjects developed treatment-emergent ADAs in the risankizumab 150 mg/mL PFS group and the risankizumab 90 mg/mL PFS group, respectively. The incidence of treatment-emergent ADAs was comparable across the two regimen arms. Of the ADA positive subjects, none of them were positive for neutralizing antibodies (NAbs).

Table 7 Incidence of ADA in Study M15-990

Group	N	Baseline ADA % (n/N)	Treatment Emergent ADA %[a] (n/N)
Risankizumab 150 mg/mL PFS	98	6.1 (6/98)	14.3 (14/98)
Risankizumab 90 mg/mL PFS	96	3.1 (3/96)	11.6 (11/95)[b]

a. Treatment emergent ADA was defined when a subject was (1) ADA negative or missing assessment at baseline (prior to the first risankizumab dose) and became ADA positive at one or more time points post baseline; or (2) ADA positive at baseline and showed a 4-fold or greater increase in titer values relative to baseline.
b. One subject did not have a post-baseline ADA sample: N = 95.

Cross reference: Study M15-990 CSR (R&D/19/1114)

- ***Study M15-999***

M15-999 is a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of risankizumab using a new formulation (150 mg/mL) in adult subjects with moderate to severe plaque psoriasis. Eligible subjects were randomized in a 2:1 ratio to risankizumab 150 mg/mL PFS or placebo PFS. Each subject received 3 self-administered SC doses given at Weeks 0, 4, and 16.

Sixteen percent (16/100) of the evaluable subjects who received at least 1 dose of risankizumab developed treatment-emergent ADAs, with none of these subjects testing positive for NAbs.

Reviewer's note: *A comparison of immunogenicity rates between the current sBLAs and original BLA is infeasible as two different immunogenicity assays were used in both submissions (see Section 6.3.4 for detailed information).*

Impact of immunogenicity on pharmacokinetics

A comparison of risankizumab trough serum concentrations by ADA status (positive or negative) at Week 16 are presented in Table 8. The results showed that development of ADAs appeared to be associated with lower risankizumab serum exposure compared to those in ADA-negative subjects.

Table 8 Risankizumab Concentrations by ADA Status in Study M15-999

	Geometric Mean (Arithmetic Mean, %CV) [Range]	
	Week 16	
	ADA Positive (N = 16)	ADA Negative (N = 79)
Risankizumab Trough Serum Concentrations (µg/mL)	0.971 (1.36, 76) [0.15 – 3.94]	1.65 (2.21, 69) [< 0.01 – 6.58]

%CV = coefficient of variance; ADA = antidrug antibody; N = sample size

Note: Subjects who had both risankizumab concentration and anti-drug antibody assessment at each visit are included in this summary.

Cross reference: Study M15-999 CSR Table 17 (R&D/20/0007)

Reviewer's note: *Geometric mean trough concentration of risankizumab at Week 16 was 1.84 µg/mL in the phase 3 trials of BLA 761,105 (90 mg/mL). The mean risankizumab concentrations in subjects who had ADA titer values ≥128 were approximately 30% lower compared with the concentrations in ADA negative subjects. In addition, different bioanalytical methods were applied in the original BLA 761,105 and the current sBLAs (see Section 6.3.4 for detailed information).*

Impact of immunogenicity on efficacy

The comparison of PASI 90 and sPGA 0/1 responses at Week 16 by ADA status (positive or negative) are summarized in Table 9. PASI 90 and sPGA 0/1 responses at Week 16 were comparable between subjects who were ADA positive and those who are ADA negative.

Table 9 PASI 90 and sPGA 0/1 Responses by ADA Status at Week 16 in Study M15-999

Efficacy Response (NRI)	Week 16	
	ADA Positive (N = 16)	ADA Negative (N = 84)
PASI90, N (%)	10 (62.5)	56 (66.7)
sPGA 0/1, N (%)	14 (87.5)	68 (81.0)

ADA = antidrug antibody; NRI = non-responder imputation; PASI 90 = achievement of ≥ 90% reduction from baseline PASI score; sPGA = Static Physician Global Assessment

Note: Subjects who had both risankizumab concentration and anti-drug antibody assessment at each visit are included in this summary.

Cross reference: Study M15-999 CSR Table 18 (R&D/20/0007)

Reviewer's note: *Clinical response rates at Week 16 ranged 72% to 75% for PASI 90 and 84% to 88% for sPGA 0/1 in the four Phase 3 trials of BLA 761,105 (90 mg/mL).*

6.3.4. Which bioanalytical methods were used for the determination of the concentrations of risankizumab and the immunogenicity assessment?

- ***Determination of risankizumab concentrations***

The Applicant has developed and validated three assays for measurement of risankizumab concentrations in human samples from clinical trials: a validated enzyme-linked immunosorbent assay (ELISA) and a bridging electrochemiluminescence (ECL) assay for determination of plasma concentrations, and a validated ECL assay for determination of serum concentrations. In the original BLA, risankizumab concentrations in human plasma were quantified using the plasma ELISA assay with the sensitivity of (b) (4) ng/mL. In the current sBLAs, risankizumab concentrations in human serum were quantified using the serum ECL assay with the sensitivity of (b) (4) ng/mL. Cross-validation experiments using spiked quality control (QC) and/or study samples were preformed and demonstrated full comparability between validated serum ECL and plasma ECL assays, and between validated plasma ECL and ELISA assays.

- ***Detection of ADAs and Nabs against to risankizumab***

Compared to the original BLA immunogenicity assays, a new drug bridging with an ECL immunoassay and a new cell-based NAb assay were applied for determination of ADA and NAb in the current sBLAs, respectively. Briefly, in the new assays, the serum

samples replaced plasma samples which were used in the original BLA immunogenicity assays. The validated bioanalytical methods used for detection of ADA and NAb against risankizumab are summarized in Table 10.

Table 10 Summary of Bioanalytical Methods for Detection of ADA and Nab

(b) (4)

Summary of OSIS inspection: Since the approval of the 150 mg single injection administered using the AI platform was solely based on the PK comparability study (M15-990); OSIS inspection of the bioanalytical site was requested which included inspection of bioanalytical assays as well as immunogenicity assays.

Regarding the performance and validation of the new immunogenicity assays, the OSIS reviewer observed objectionable findings in the analytical portion of Study M15-990 (*See Bioequivalence Establishment Inspection Report Review dated 2/16/2021 from Dr. Kara Scheibner in DARRTS, Reference ID: 4747601*). With regards to the issues with the immunogenicity assay, we consulted with OBP by email. See comments below from Dr. Riley Myers on 2/24/2021:

1) *Are the new immunogenicity assays adequate for determination of ADA and NAb in sBLAs?*

The results from validation studies (Section 5.3.1.4) support that both assays for detection of binding and neutralizing ADAs are suitable for their intended use in the analysis of clinical samples. The assays are sensitive, specific, selective, precise, robust and tolerant to onboard drug levels.

2) *Can we compare immunogenicity results obtained from two different assays?*

It is not possible to compare the immunogenicity results obtained from different assays because of differences in assay parameters (e.g. assay sensitivity, tolerance etc.),

assay procedures, samples and controls used in the assay validation study, and in the analysis of clinical samples. Data to support method bridging were not provided in the submission (e.g. analysis of the sample with both assay versions), and therefore it is not possible to make any claims regarding method comparability. In principle, when a direct comparison of immunogenicity rates is needed, the samples should be obtained from the head-to-head clinical study and should be tested using assays that have been demonstrated to have equivalent sensitivity and specificity.

3) *There are some issues identified in inspection. Could you please let us know the impact of this?*

- *Item 1- During ADA sample analysis, 470 samples were assessed in the presence of drug concentrations exceeding the validated tolerance of the ADA assay (4684ng/mL of risankizumab in serum).*

This is a concern noted by the OSIS reviewer because it could result in masking of samples that are truly positive, leading to misclassification as ADA negative samples. However, the results from the validation study evaluated positive control samples at 100 ng/mL, which is within the clinically relevant ADA range known to elicit a clinically meaningful response. The results showed that the assay can tolerate up to 23.6 mcg/mL risankizumab, which is above the expected Cmax from M15990 study (20.1 mcg/mL). Given that the intended use of the screening assay is to identify potentially positive samples ("screen positive") using 5% false positive rate, the objectionable observation does not impact validation of the assay. Clinical samples showed ~30% false positive rate, which is significantly above the expected 2-11% and not consistent with any significant masking of potentially positive samples. The OSIS reviewer acknowledged this but also noted that in real-time analysis of ADA samples, an ECL readout from a majority of ADA concentrations is closer to 6 ng/mL than to 100 ng/mL and that there was an inverse correlation between the raw ECL values and on-board drug concentration, suggesting that there could have been interference. Nevertheless, even if there was interference, potentially positive samples were still detectable at the ECL values below that corresponding to the 100 ng/mL positive control signal, and thus above the screening cut-point signal.

- *Item 2-During ADA sample analysis, samples in run 40 were repeated inadvertently in run 176. Results from the inadvertent re-assay in run 176 were used to determine the final reported result despite obtaining valid results in run 40.*

The impact on study validity is unlikely because all results from a repeated run were comparable and acceptable. The issue was handled by updating the SOP.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Studies M15-990, M15-999, and M16-005 were submitted in support of the new formulation/ device and are shown in Table 11.

Table 11: Table of Clinical Studies

Study ID/ No. of Centers/ Locations/ Duration	Study Start/ Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Group Entered/ Completed All Study Visits*	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M15-990/ 2 centers/ US/ 113 days	April 2019/ completed, April 2020/ 226/231	Phase 1, single-dose, randomized, 3-parallel-arm, open-label	150 mg/mL SC PFS: single dose 90 mg/mL SC PFS: single dose 150 mg/mL SC AI: single dose	To assess the bioavailability of risankizumab 150 mg/mL formulation in PFS relative to 90 mg/mL formulation in PFS and to assess the bioavailability of risankizumab 150 mg/mL formulation in AI relative to 150 mg/mL formulation in PFS	150 mg/mL PFS: 98/98 90 mg/mL PFS: 96/93 150 mg/mL AI: 32/32	129/97 36.0 years (18, 56)	Adults with body weight less than 110 kg; no previous exposure to any anti-IL-12/23 or anti-IL-23 treatment; no intention to perform strenuous exercise to which the subject is unaccustomed within 1 week prior to administration of study drug or during the study.	90% confidence intervals from the analyses of the natural logarithms of C_{max} and AUC are within the 0.80 to 1.25 range.

Study ID/ No. of Centers/ Locations/ Duration	Study Start/ Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Group Entered/ Completed All Study Visits[a]	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M15-999/ 38 centers/ US/ 196 days	May 2019/ completed, October 2019/ 157/150	Phase 3, randomized, double-blind, placebo-controlled	Risankizumab: 150 mg/mL SC PFS at Wks 0, 4, and 16 Placebo: SC PFS Wks 0, 4, and 16	Evaluate the efficacy and safety of the 150 mg/mL formulation of risankizumab in a PFS compared with placebo for the treatment of adult subjects with moderate to severe plaque psoriasis.	As of interim data cutoff date of 20 February 2020: Risankizumab: 105/5 (93 ongoing at data cutoff) Placebo: 52/2 (30 ongoing at data cutoff)	87/70 50.0 years (19, 79)	Adult subjects with stable moderate to severe plaque psoriasis, defined as ≥ 10% body surface area (BSA) psoriasis involvement, sPGA score of ≥ 3, and PASI ≥ 12 at Screening and Baseline visits.	PASI 90 and sPGA clear or almost clear at Wk 16

Study ID/ No. of Centers/ Locations/ Duration	Study Start/ Enrollment Status, Date Total Enrollment/ Enrollment Goal	Design Control Type	Study & Control Drugs Dose, Route & Regimen	Study Objective	No. of Subjects by Group Entered/ Completed All Study Visits[a]	Gender M/F Median Age (Range)	Diagnosis Inclusion Criteria	Primary Endpoints
M16-005/ 24 centers/ US/ 280 days	June 2019/ completed, September 2019/ 108/100	Phase 3, single-arm, open-label	Risankizumab: 150 mg/mL SC AI at Wks 0, 4, 16, and 28	Evaluate the usability of the combination product of RZB in an AI, as well as to evaluate the efficacy, safety, and tolerability of RZB administered by AI for the treatment of adult patients with moderate to severe plaque psoriasis.	As of interim data cutoff date of 13 April 2020: Risankizumab: 108/1 (102 ongoing at data cutoff)	66/42 48.5 years (19, 78)	Adult subjects with stable moderate to severe plaque psoriasis, defined as ≥ 10% body surface area (BSA) psoriasis involvement, sPGA score of ≥ 3, and PASI ≥ 12 at Screening and Baseline visits.	- PASI 75/90/100, sPGA clear, and sPGA clear or almost clear at Wk 16 - Observer rating of successful subject self-administration and no potential hazards at Week 0 and 28 - Subject rating of acceptability at each visit collected

AI = autoinjector; AUC = area under the concentration-time curve; Cmax = maximum observed concentration; IL = interleukin; PASI = Psoriasis Area Severity Index; PFS = prefilled syringe; SC = subcutaneous; US = United States

7.1.2. Review Strategy

The sources of data included final study reports submitted by the applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)]. This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format were in the following network path:

Original submission:
\\CDSESUB1\evsprod\bla761105\0074\m5\datasets\m15-999\analysis
\\CDSESUB1\evsprod\bla761105\0079\m5\datasets\m16-005\analysis\

Data and Analysis Quality

In general, the data submitted by the applicant to support the efficacy of risankizumab appeared adequate.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study Design and Endpoints

The applicant conducted two Phase 3 trials (M15-999, M16-005) to support the application.

For both trials, the key inclusion criteria that defined the study population were identical and are as follows:

- Male or female 18 years of age or older
- Diagnosis of plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug
- Stable moderate to severe chronic plaque-type psoriasis with or without psoriatic arthritis at both screening and baseline (randomization):
  - Static Physician Global Assessment (sPGA) score of at least 3 (moderate). The protocol-specified sPGA scale is shown below.

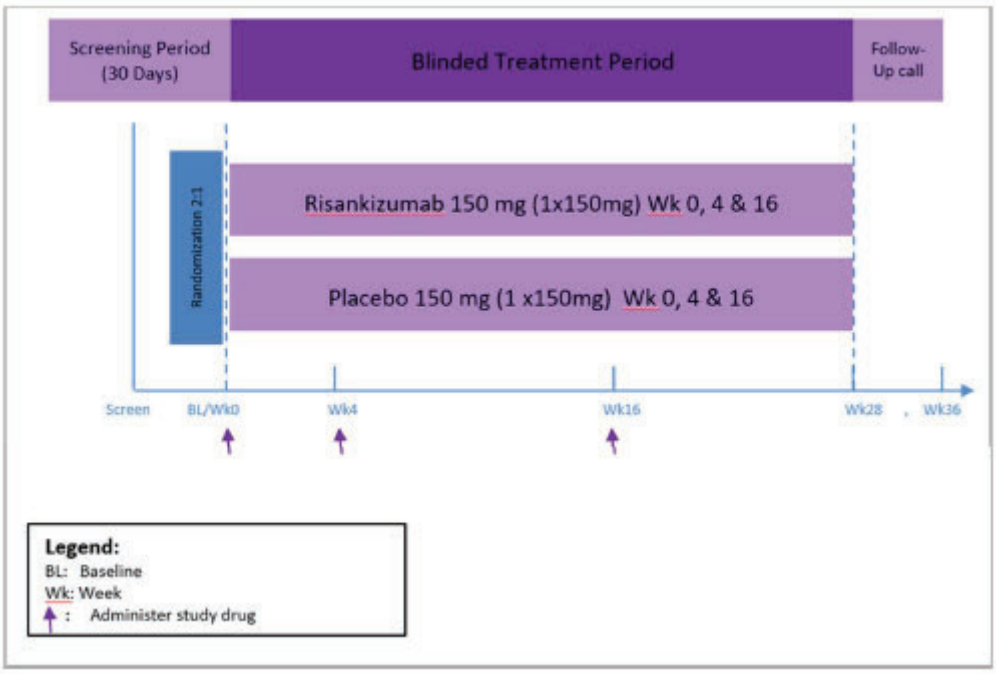
Score	Short Description	Detailed Description
0	clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present.
1	almost clear	Normal to pink coloration. Just detectable (possible slight elevation above normal skin). No to minimal focal scaling.
2	Mild	Pink to light red coloration. Mild thickening (slight but definite elevation, typically edges are indistinct or sloped). Predominantly fine scaling.
3	moderate	Dull to bright red coloration. Clearly distinguishable to moderate thickening. Moderate scaling.
4	severe	Bright to deep dark red coloration. Severe thickening with hard edges. Severe coarse scaling covering almost all or all lesions.

Source: Applicant's protocol (Appendix D)

- Psoriasis Area and Severity Index (PASI) ≥12
- Body Surface Area (BSA) ≥10%

Trial M15-999 was a multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of risankizumab using a new formulation (prefilled syringe 150 mg/mL). Figure 7.2.1.1 presents the study design schematic for Trial M15-999.

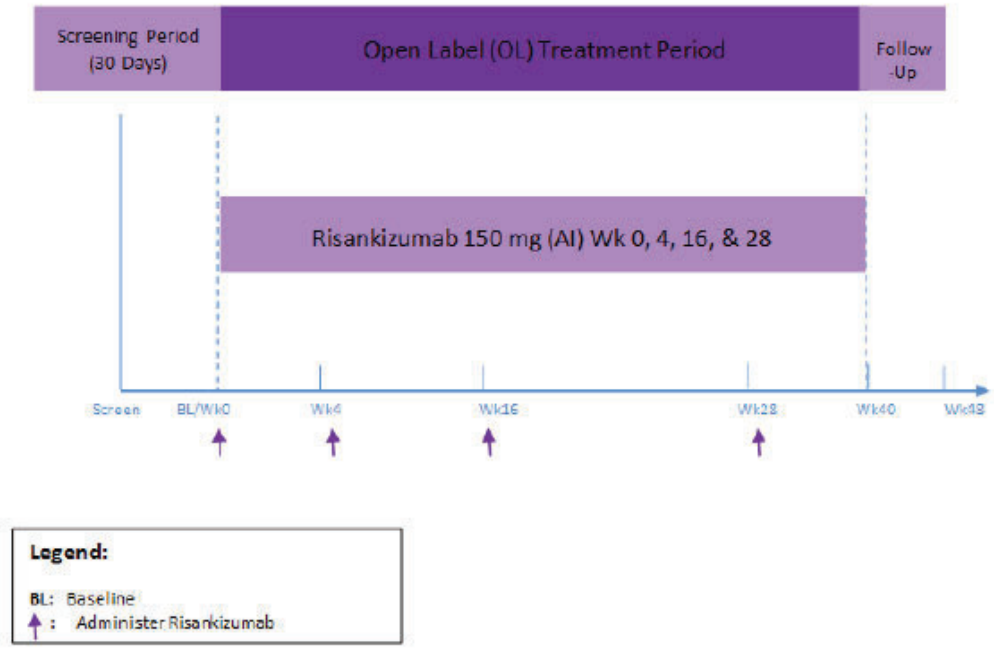
Figure 7.2.1.1 Study Design Schematic for M15-999



Source: Applicant's study report for M15-999 (Figure 1)

Trial M06-005 was a single-arm, open-label usability study using the autoinjector. The study design schematic is shown in Figure 7.2.1.2.

Figure 7.2.1.2. Study Design Schematic for M16-005



Source: Applicant's study report for M16-005 (Figure 1)

Both trials consisted of the following periods: a screening period, a treatment period (Weeks 0 to 28 for M15-999; Weeks 0 to 40 for M16-005), and a follow-up period. Note that as M16-005 was a single-arm, open-label study, summary of study design and analysis in this section mainly focus on Trial M15-999, and the results for M16-005 are reported in this section for completion.

For the 28-week treatment period in M15-999, a total of 157 subjects were randomized in a 2:1 ratio to the following arms:

- Risankizumab PFS 150 mg/mL self-administered at Weeks 0, 4, and 16 (105 subjects)

- Matching Placebo self-administered at Weeks 0, 4, and 16 (52 subjects)

Subjects were evaluated at screening, baseline (Day 1), Weeks 4, 16, 28, and telephone follow-up at 20 weeks after the last dose of the study drug.

The protocol-specified the following co-primary efficacy endpoints:

- Proportion of subjects who achieved ≥90% reduction from baseline PASI (PASI 90) at Week 16

- Proportion of subject who achieved an sPGA score of clear or almost clear (0 or 1) at Week 16

Secondary endpoints were the following:

- Proportion of subjects who achieved PASI 100 at Week 16
- Proportion of subjects who achieved sPGA clear (score of 0) at Week 16

7.2.2. Statistical Methodologies

The primary analysis population was the Intent to Treat (ITT) population defined as all randomized subjects.

For the analysis of the co-primary endpoints and the binary secondary endpoints in Trial M15-999, the protocol specified using the Chi-square test. The protocol specified testing the endpoints in a hierarchical order by testing the co-primary endpoints first followed by the ranked secondary endpoints to control the Type I error rate (two-sided, α=0.05), and only if the two co-primary endpoints are statistically significant, the secondary endpoints would be tested.

For handling of missing data, the protocols specified using No Response Imputation (NRI) approach and consider the missing data as failures. For sensitivity analyses for handling missing efficacy data, the protocols specified using the “as-observed” analysis without imputing for missing assessments.

7.2.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

M15-999 randomized a total of 157 subjects from 38 US centers. Trial M16-005 enrolled a total of 108 subjects from 28 US centers. Table 7.2.3.1 presents the disposition of subjects of Trials M15-999 and M16-005. For M15-999, the discontinuation rates were 7% and 39% in risankizumab and placebo arms, respectively. Note that as the majority of the subjects that discontinued in the placebo arm (i.e., 11 of the 20) was due to lack of efficacy, the primary imputation method of using the non-responder imputation appear reasonable.

Table 7.2.3.1. Subject Disposition for Trials M15-999 and M16-005

	M15-999			M16-005
	Risankizumab	**Placebo**	**Total**	**Risankizumab**
Randomized	105	52	157	108
Discontinued	7 (7%)	20 (39%)	27 (17%)	5 (5%)

Reasons for discontinuation				
Adverse Events	0 (0%)	1 (2%)	1 (<1%)	1 (1%)
Withdrew Consent	3 (3%)	6 (12%)	9 (6%)	0
Lost to follow-up	4 (4%)	2 (4%)	6 (4%)	1 (1%)
Lack of efficacy	0 (0%)	11 (21%)	11 (7%)	1 (1%)
Other	-	-	-	0 (0%)

Source: Applicant's Study Report (Table 14.1.2)

The baseline demographics and baseline disease characteristics are presented in Tables 7.2.3.2 and 7.2.3.3, respectively. The baseline demographics were generally balanced across the treatment arms in M15-999. In Trial M15-999, approximately 55% of the subjects were male, 83% of the subjects were White, 83% of subjects were 19-64 years of age. Similar baseline demographic trends were observed in M16-005 where approximately 61% of the subjects were male, 88% of subjects were White, and approximately 79% of subjects were 19-64 years of age.

Table 7.2.3.2. Baseline Demographics for Trials M15-999 and M16-005

	M15-999			**M16-005**
	Risankizumab N=105	**Placebo N=52**	**Total N=157**	**Risankizumab N=108**
Age				
Mean	49.3	48.8	49.1	49.2
SD	15.14	15.47	15.20	14.32
Median	50.0	54.0	50.0	48.5
Range	19-79	21-78	19-79	19-78
<65	86 (82%)	44 (85%)	130 (83%)	85 (79%)
≥65	19 (18%)	8 (15%)	27 (17%)	23 (21%)
Sex				
Female	46 (44%)	24 (46%)	70 (45%)	42 (39%)
Male	59 (56%)	28 (54%)	87 (55%)	66 (61%)
Race				
White	87 (83%)	44 (85%)	131 (83%)	95 (88%)
Black	12 (11%)	4 (8%)	16 (10%)	5 (5%)
Asian	3 (3%)	1 (2%)	4 (3%)	7 (6%)
Other	3 (3%)	3 (5%)	4 (3%)	1 (1%)

Source: Reviewer Table; Applicant's table 14.1__3

The baseline disease characteristics were generally balanced across the treatment arms in M15-999. Approximately 84% of subjects were moderate severity in sPGA, and the mean and median PASI at baseline were about 21.37 and 18.00, respectively. Similar baseline disease characteristics were observed for those in trial M16-005 where approximately 82% of subjects were sPGA of 3 at baseline, and the mean and median PASI at baseline were 19.83 and 17.55, respectively.

Table 7.2.3.3. Baseline Disease Severity for Trials M15-999 and M16-005

	M15-999			M16-005
	Risankizumab N=105	**Placebo N=52**	**Total N=157**	**Risankizumab N=108**
sPGA				
Moderate (3)	86 (82%)	46 (89%)	143 (84%)	88 (82%)
Severe (4)	19 (18%)	6 (11%)	25 (16%)	20 (18%)
PASI				
mean	21.53	21.06	21.37	19.83
SD	9.60	10.26	9.79	7.24
Median	18.00	18.2	18.0	17.55
Range	12.2-68.6	12.0-72.0	12.0-72.0	12.10-51.20
BSA				
Mean	28.34	28.16	28.28	25.47
SD	16.41	18.49	17.07	17.47
median	24.10	23.00	24.00	19.00
range	10.00-90.00	11.00-95.00	10.00-95.00	10.00-98.00

Source: Reviewer Table; Applicant's tables 14-1.

7.2.4. Results for the Co-primary Efficacy Endpoints

Table 7.2.4.1 presents the results for the co-primary efficacy endpoints at Week 16 for Trial 15-999. Results for Trial M16-005 are also reported. Risankizumab was statistically superior to placebo (p-values<0.001) for both co-primary efficacy endpoints in Trial M15-999.

Table 7.2.4.1. Proportion of subjects who achieved PASI 90, and sPGA 0 or 1 at Week 16 in Trials 15-999 and 16-005 (Co-primary Endpoints; Non-responder imputation, ITT)

	M15-999			M16-005
	Risankizumab	**Placebo**	**p-value (1)**	**Risankizumab**
Randomized	105	52		108
PASI 90	66 (63%)	2 (4%)	<0.001	72 (67%)
sPGA 0 or 1	82 (78%)	5 (10%)	<0.001	88 (82%)

Source: Reviewer's Table; (1) P-value was calculated using the Fisher's Exact Test

7.2.5. Results for the Secondary Efficacy Endpoints

Table 7.2.5.1 presents the results for the ranked secondary efficacy endpoints for Trial 15-999, and the table also includes the results for Trial M16-005. In M15-999,

risankizumab was statistically superior to placebo with p-values<0.001 in the overall population for all the secondary efficacy endpoints. PASI 100 responses at Week 16 and sPGA 0 scores at Week 16 for those that received risankizumab were slightly higher in the open-label Trial M16-005.

Table 7.2.5.1. Proportion of subjects who achieved PASI 100, and sPGA 0 at Week 16 in Trials 15-999 and 16-005 (Secondary Endpoints; Non-responder imputation, ITT)

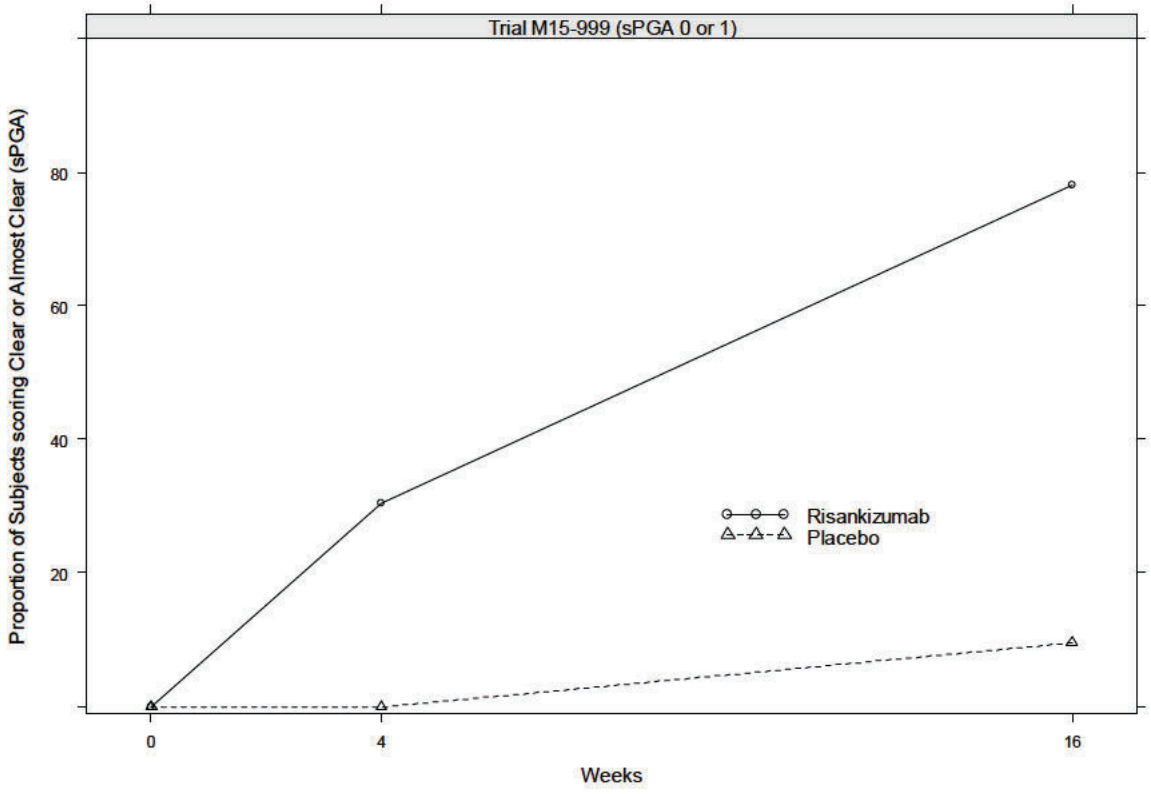
	M15-999			M16-005
	Risankizumab	**Placebo**	**p-value (1)**	**Risankizumab**
Randomized	105	52		108
PASI 100	40 (38%)	1 (2%)	<0.001	50 (46%)
sPGA 0	41 (39%)	1 (2%)	<0.001	51 (47%)

Source: Reviewer's Table; (1) P-value was calculated using the Fisher's Exact Test

7.2.6. Efficacy Over Time

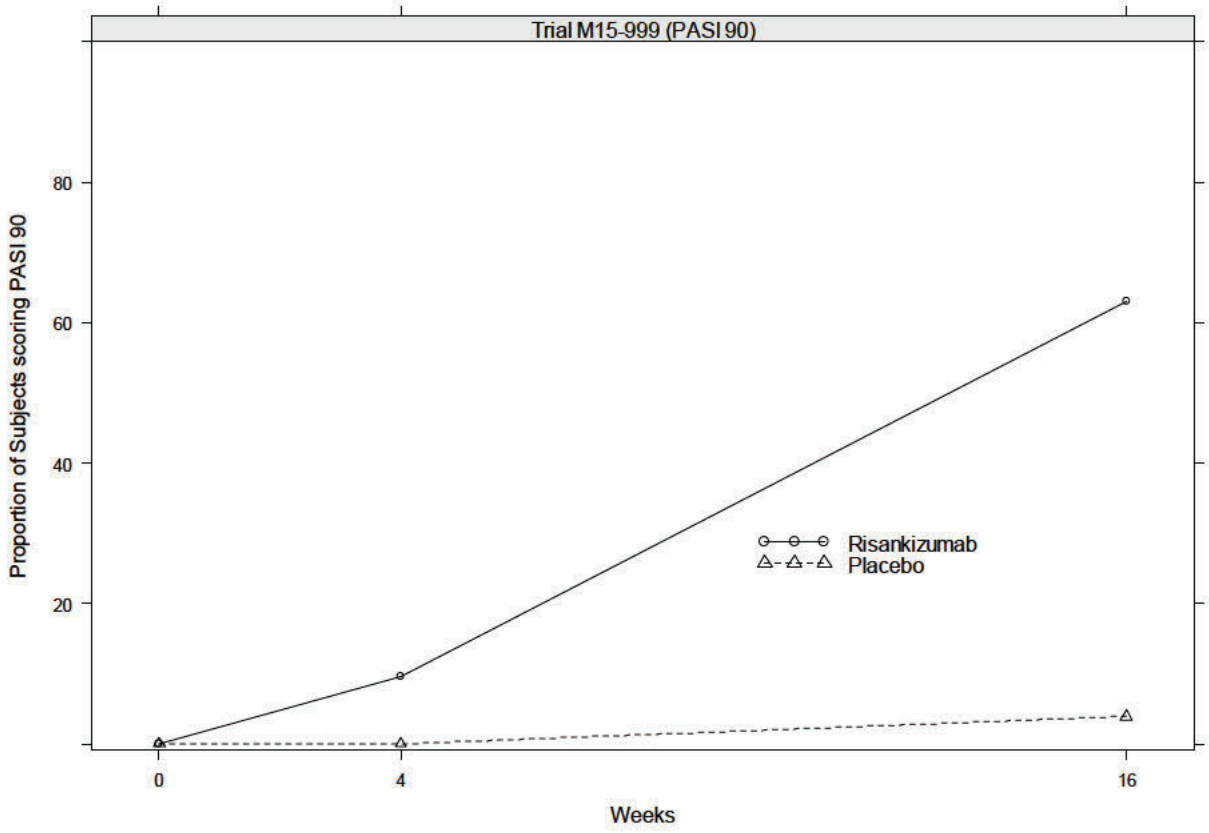
Figures 7.2.6.1 and 7.2.6.2 present the results for sPGA 0 or 1 and PASI 90, respectively, through Week 16 for Trial M15-999.

Figure 7.2.6.1. Results for sPGA score of 0 or 1 Through Week 16 for Trial M15-999



Source: reviewer figure; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI).

Figure 7.2.6.2. Results for PASI 90 Through Week 16 for Trial M15-999



Source: reviewer figure; Intent-to-Treat (ITT) analysis set; Missing data was imputed using non-responder imputation (NRI).

7.2.7. Findings in Special/Subgroup Populations

Table 7.2.7.1 presents the results for the co-primary efficacy endpoint of sPGA score of 0 or 1 at Week 16 by sex, age (<65, ≥65 years), race (White, Black, Asian, Other), and baseline sPGA severity for Trial M15-999 and M16-005. Results were generally consistent across subgroup populations; however, note that racial subgroups other than White were limited in number.

Table 7.2.7.1. sPGA 0 or 1 at Week 16 by Sex, Age, Race, and baseline sPGA for Trials M15-999 and M16-005

	M15-999		M16-005
	Risankizumab N=105	Placebo N=52	Risankizumab N=108
Age			
<65	69/86 (80%)	4/44 (9%)	73/85 (86%)
≥65	13/19 (68%)	1/8 (13%)	15/23 (65%)
Sex			
Female	32/46 (70%)	3/24 (13%)	34/42 (81%)

Male	50/59 (85%)	2/28 (7%)	54/66 (82%)
Race			
White	68/87 (78%)	5/44 (11%)	78/95 (82%)
Black	9/12 (75%)	0/4 (0%)	4/5 (80%)
Asian	3/3 (100%)	0/1 (0%)	5/7 (71%)
Other	2/3 (67%)	0/3 (0%)	1/1 (100%)
sPGA			
Moderate (3)	70/86 (81%)	5/46 (11%)	79/88 (89%)
Severe (4)	12/19 (63%)	0/6 (0%)	9/20 (45%)

Source: reviewer table

Table 7.2.7.2. PASI 90 at Week 16 by Sex, Age, Race for Trials M15-999 and M16-005

	M15-999		M16-005
	Risankizumab N=105	**Placebo N=52**	**Risankizumab N=108**
Age			
<65	57/86 (66%)	2/44 (5%)	60/85 (71%)
≥65	9/19 (47%)	0/8 (0%)	12/23 (52%)
Sex			
Female	26/46 (57%)	1/24 (4%)	26/42 (62%)
Male	40/59 (68%)	1/28 (4%)	46/66 (70%)
Race			
White	54/87 (62%)	2/44 (5%)	65/95 (68%)
Black	8/12 (67%)	0/4 (0%)	3/5 (60%)
Asian	2/3 (67%)	0/1 (0%)	4/7 (57%)
Other	2/3 (67%)	0/3 (0%)	0/1 (0%)
sPGA			
Moderate (3)	55/86 (64%)	2/46 (4%)	63/88 (72%)
Severe (4)	11/19 (58%)	0/6 (0%)	9/20 (45%)

Source: reviewer table

7.3. Review of Safety

7.3.1. Safety Review Approach

Safety was evaluated in Studies M15-999 and M16-005 by the monitoring of adverse events (AEs), the evaluation of clinical laboratory values (hematology and clinical chemistry) and vital signs. In analyses of all treatment-emergent AEs (TEAEs), some categories of AEs were considered to be areas of safety interest and were identified:

- infections (which includes serious infections, active tuberculosis (TB), opportunistic infections, and fungal infections)
- injection-site reactions
- hypersensitivity and anaphylactic reactions
- hepatic events
- malignancies (including malignant tumors, nonmelanoma skin cancer [NMSC], and malignant tumors excluding NMSC)
- cardiovascular (CV) events (including major adverse cardiovascular events (MACE) and extended MACE)

In Trial M15-999, subjects treated with the 150mg/ml formulation were compared to placebo treated subjects for up to 28 weeks. Interim data was provided with the submission and the remainder of the safety data was submitted in the safety update report. Trial M16-005 was an open-labelled study and safety data was assessed in the context of the characterized safety data from the 90 mg/mL formulation.

7.3.2. Review of the Safety Database

Overall Exposure

In Study M15-990: 226 subjects were randomized to receive one risankizumab Injection.
In Study M15-999: 105 subjects were exposed to at least 1 dose of risankizumab 150 mg with a median duration of 164 days (as of the interim data cutoff of 20 February 2020).
In Study M16-005: 108 subjects were exposed to at least 1 dose of risankizumab 150 mg with a median duration of 243 days of exposure (as of the interim data cutoff for of 13 April 2020).
The SUR provides for approximately 5 months of additional safety data for both completed 36-week Study M15-999 and completed 48-week Study M16-005.

Relevant characteristics of the safety population:

The populations across the studies were balanced across treatment groups with respect to gender, race, weight, and age No clinically meaningful differences in demographics were identified.

Adequacy of the safety database:

The clinical studies (which includes one open-labelled study) were mainly supportive in the demonstration the comparability between the approved and new formulation. The safety database appears adequate for this intent.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the applicant.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities MedDRA) version 22.1. Each AE was coded to a system organ class (SOC) and preferred term (PT). Severity of the AEs was assessed using Common Terminology Criteria for Adverse Events (CTCAE) criteria. The coding of adverse events in the sBLA submission appeared adequate and allowed for estimation of AE risks.

Routine Clinical Tests

Vital signs and physical findings were evaluated. Hematology, clinical chemistry, and liver function tests were performed. Laboratory test values was assessed using CTCAE version 4.03

7.3.4. Safety Results

Deaths

No deaths were reported during Study M15-990 or through the data cutoffs for Studies M15-999 and M16-005. No deaths were reported upon completion of the trials as per the SUR.

Serious Adverse Events

In Study M15-999 one subject (1%) reported a SAEs (pancreatitis). The event of acute pancreatitis occurred in a subject treated with risankizumab and a medical history of chronic pancreatitis.

In the interim data for Study M16-005, five subjects (4.6%) reported SAEs (Atrial fibrillation, pyrexia, pyelonephritis, thermal burn and lumbar spinal stenosis). In the completed study, serious adverse events were reported in 6 (5.6%) subjects (7 events [7.3 E/100 PY]). There were 2 additional SAEs (appendicitis and prostatitis) reported.

None of the SAEs in the risankizumab-treated group led to study drug discontinuation.

For the trials conducted with the 150mg/mL formulation, there were few SAEs and no

new safety signal has been identified. The rate of SAEs appears to be comparable with the trial data evaluating the 90 mg/ mL formulation which showed that after 52 weeks of exposure, 7.0% subjects in the risankizumab group reported SAEs.

Dropouts and/or Discontinuations Due to Adverse Effects

A total of 157 subjects were randomized in Study M15-999 As of the data cutoff for the interim report, a total of 27 subjects discontinued the study prematurely, 20 subjects from the placebo group and 7 subjects from the risankizumab group. No subjects in the risankizumab 150 mg treatment group discontinued study drug due to AEs. One subject (1.9%) in the placebo group reporting an AE leading to discontinuation of study drug (large intestine infection).

A total of 108 subjects were dosed in psoriasis Phase 3 Study M16-005. As of the data cutoff for the interim report, 5 subjects discontinued the study prematurely. One subject discontinued study drug due to an AE. The subject (b) (6) is a 72 year old white male with a 2-year history of chronic kidney disease who experienced worsening of chronic kidney disease (grade 3) 33 days after last treatment. The AE was determined by the investigator to not be related to study drug and the AE status is reported as ongoing.

In the SUR, no additional subjects were reported to have discontinued the study due to an AE.

Significant Adverse Events

In Study M15-999 there was 1 subject in the risankizumab treatment group who experienced an AE that was assessed as severe (CTCAE ≥ Grade 3). This case of acute pancreatitis was characterized as a SAE and is described above.

In Study M16-005 there were 8 subjects (7.4%) who experienced AEs that were assessed as severe (CTCAE ≥ Grade 3). These AEs by preferred terms included Chest pain, Pyrexia, Appendicitis, Corona virus infection, Pyelonephritis, Ankle fracture and Thermal burn which were characterized as Grade 3 and Atrial fibrillation characterized as Grade 4.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment-emergent AEs (TEAEs) were defined as events with onset or worsening after the first dose of study drug and within 20 weeks (140 days) after the last dose of study drug.

Study M15-999
As of the data cutoff date of Study M15-999, a total of 20 subjects in the risankizumab 150 mg/mL group experienced at least 1 AE (19.0%, 46 events [95.2 E/100 PY]), as compared to 11 subjects (21.2%, 16 events [69.0 E/100 PY]) in the placebo group

Table 12: Adverse Events Reported in > 1% of Subjects in Study M15-999

MedDRA 22.1 Preferred Term	PBO (N = 52) (PY = 23.2)		RZB (N = 105) (PY = 48.3)	
	n (%)	E (E/100 PY)	n (%)	E (E/100 PY)
Any adverse event	11 (21.2)	16 (69.0)	20 (19.0)	46 (95.2)
Nasal congestion	0	0	3 (2.9)	3 (6.2)
Nausea	1 (1.9)	1 (4.3)	3 (2.9)	3 (6.2)
Arthralgia	0	0	2 (1.9)	2 (4.1)
Hyperhidrosis	0	0	2 (1.9)	3 (6.2)
Hypertension	1 (1.9)	1 (4.3)	2 (1.9)	2 (4.1)

E = events; PBO = placebo; PY = patient-year; RZB = risankizumab

The majority of AEs observed with risankizumab treatment in Study M15-999 were mild (CTCAE Grade 1) in severity. The common AEs observed with 150 mg/ mL risankizumab treated subjects as compared to placebo appears to be generally comparable to the characterized adverse events demonstrated with the 90 mg/ mL formulation.

M16-005

As of the data cutoff date of Study M16-005, a total of 44 subjects reported at least 1 AE (40.7%, 92 events [129.2 E/100 PY]).

Table 13: Adverse Events Reported in > 2% of Subjects in Study M16-005

	RZB (N = 108) (PYs = 71.2)	
MedDRA 22.1 Preferred Term	n (%)	E (E/100 PY)
Any adverse event	44 (40.7)	92 (129.2)
Nasopharyngitis	8 (7.4)	8 (11.2)
Upper respiratory tract infection	6 (5.6)	6 (8.4)
Cough	3 (2.8)	3 (4.2)
Gastroenteritis	3 (2.8)	3 (4.2)
Diarrhoea	2 (1.9)	2 (2.8)
Fatigue	2 (1.9)	2 (2.8)
Headache	2 (1.9)	2 (2.8)
Nausea	2 (1.9)	2 (2.8)
Papule	2 (1.9)	3 (4.2)
Seasonal allergy	2 (1.9)	2 (2.8)
Sinusitis	2 (1.9)	2 (2.8)
Vomiting	2 (1.9)	2 (2.8)

E = events; PY = patient-year; RZB = risankizumab

The majority of AEs observed were mild to moderate (Common Toxicity Criteria for Adverse Events [CTCAE] Grade 1 or 2) in severity. The common AEs observed in the open label trial do not provide substantial evidence for a significantly different safety profile as compared to the safety profile characterized for the 90 mg/mL formulation.

The SUR included an additional 4 and 12 events for studies M15-999 and M16-005, respectively. After the completion of both studies, the majority of AEs observed with risankizumab treatment was generally consistent with the with the risankizumab treatment group from the original submission using the 90 mg/mL formulation.

Laboratory Findings

Mean changes from Baseline with risankizumab treatment groups were small and do not appear to be clinically meaningful. Shifts in hematology and chemistry values from Grade 0, 1, or 2 at Baseline to Grade 3 or higher during treatment were generally infrequent and do not appear to be clinically meaningful with the exception of 1 subject in Study M15-999, treated with risankizumab 150 mg/mL, who had clinically meaningful changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin values.

This subject, a 50 year old black female with a history of chronic pancreatitis, abnormal liver function tests prior to study drug dosing and on concomitant daily paracetamol, experienced an SAE of acute pancreatitis which started on treatment Day 88 and was

resolved on Day 94. This subject also had changes in ALT and AST ≥ 3-fold upper limit of normal (ULN) at the beginning of the follow-up period (treatment Day 196) which resolved at the next visit and a reoccurring ALP ≥ 2-fold ULN since Baseline.

Vital Signs

The proportion of subjects in Studies M15-999 and M16-005 treated with risankizumab 150 mg/mL who had potentially clinically important vital sign abnormalities was low.

Immunogenicity

Immunogenicity to the risankizumab 150 mg/mL formulation did not appear to impact the overall safety profile including reported hypersensitivity and injection site reactions.

7.3.5. Analysis of Submission-Specific Safety Issues

Serious infections

No events of serious infection or fungal infection were reported in either treatment group in Study M15-999.

In Study M16-005, the proportion of subjects with serious infection AEs is low. Serious infections (PTs: appendicitis and pyelonephritis) were reported in 2 (1.9%) subjects. These subjects did not discontinue study drug due to the serious infections. Mild fungal infection (PT: fungal skin infection) was reported in 1 subject (0.9%). This subject did not discontinue study drug due to the AE.

Injection Site Reactions

No events of injection site reaction were reported in Study M16-005. The proportion of subjects in the risankizumab group of Study M15-999 who had injection site reaction AEs was low. One subject (1.0%) in the risankizumab group reported a mild AE of injection site reaction which did not lead to discontinuation of study drug. This subject was antidrug antibody (ADA) negative.

Hypersensitivity Reactions

The proportion of subjects in the risankizumab group in Study M15-999 who had a hypersensitivity AE was low (1.0%).The subject in the risankizumab group who experienced a hypersensitivity reaction reported a non-serious AE of lip swelling which did not lead to discontinuation of study drug. The subject who reported this mild AE of lip swelling was the same ADA negative subject who reported the non-serious, mild AE of injection site reaction.

The proportion of subjects in Study M16-005 who had a hypersensitivity AE was low (2.8%). The 3 subjects who experienced hypersensitivity reactions reported non-serious, mild AEs of dermatitis contact and drug hypersensitivity (with a reported term of allergic reaction to terbinafine) and a moderate AE of rash. None of these AEs were considered by the investigator to have a reasonable possibility of being related to risankizumab and none led to discontinuation of study drug.

Hepatic Events
No hepatic events were reported in Study M16-005.

A total of 1 (1.0%) subject in the risankizumab group reported a total of 2 hepatic AEs. Both events were mild (CTCAE Grade 1) for ALT increased and AST increased.

7.3.6. Safety Analyses by Demographic Subgroups

The safety study population in trial M15-999 did not have clinically meaningful differences in demographics, disease characteristics, or medical history between treatment groups that would have influenced the safety conclusions and had similar demographics to the study population of trial M16-005.

Generally, there did not appear to be substantial differences in the risk of adverse reactions in any given demographic subgroup. However, because the trials were not powered for these analyses, the data must be interpreted with caution.

7.3.7. Specific Safety Studies/Clinical Trials

A human factors (HF) validation study report and labels and labeling were submitted under BLA 761105 Supplement 9 for the proposed pre-filled syringe (PFS) device. The study was reviewed by DMEPA (see 6/26/20 review by Madhuri R. Patel, PharmD). Labeling modifications were recommended to address the use errors identified.

The Applicant submitted revised Instructions for Use (IFU) received on March 22, 2021 and April 7, 2021 and carton labeling and cardboard sleeve labeling received on March 19, 2021 for Skyrizi. DMEPA finds the carton labeling, cardboard sleeve labeling, and IFU are acceptable from a medication error perspective (see 4/13/21 memorandum by Madhuri R. Patel, PharmD).

7.3.8. Additional Safety Explorations

No additional safety explorations were conducted to evaluate the new 150 mg/mL formulation.

7.3.9. Safety in the Postmarket Setting

The 150 mg/mL formulation of risankizumab has not been approved for use in any country.

As of 25 March 2020, risankizumab 90 mg/mL formulation is approved in 55 countries worldwide. The worldwide postmarketing patient exposure to risankizumab was estimated to be 23,191 patient treatment years since the International Birth Date (26 March 2019).

Review of postmarketing data submitted in periodic safety update reports do not appear to reveal any new safety concerns.

7.3.10. Integrated Assessment of Safety

In both trials evaluating the 150 mg/mL formulation of risankizumab, no adjudicated cardiovascular events, active TB infections, fungal infections, opportunistic infections, malignancies, or adjudicated suspected anaphylaxis/anaphylactic reactions were reported.

The rates of hypersensitivity reactions and injection site reactions were low in the risankizumab 150 mg/mL treatment group. Immunogenicity and antidrug antibodies to the risankizumab 150 mg/mL formulation did not appear to have an impact on the overall safety profile including reported hypersensitivity and injection site reactions.

The rates of serious infection, fungal infection, and hypersensitivity events were low.

The profile of adverse drug reactions appears unchanged for the 150 mg/mL formulation based on the review of AE data. No new safety risks or signals are identified based on the laboratory or vital sign data. The safety profile of 150 mg/mL formulation and 90 mg/mL appear comparable. Overall, the data presented support the risankizumab 150 mg/mL formulation administered with the PFS and AI has an acceptable safety profile as a treatment for moderate to severe plaque psoriasis in adult patients moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects were large and generally consistent across endpoints. For M15-999, the discontinuation rates were 7% and 39% in risankizumab and placebo arms, respectively. Note that the majority of the subjects that discontinued in the placebo arm (i.e., 11 of the 20) was due to lack of efficacy, therefore, the primary imputation method of using the non-responder imputation appear reasonable. Furthermore, it should be noted that placebo responses for biologic for this indication is generally very low (i.e., <5%). In the original submission (BLA 761105), the placebo response rates were 2 to

8% in the two pivotal trials (Trials 1311.28 and M16-008) for the co-primary endpoints. In addition, given the high observed response rates for risankizumab, both in the pivotal trials as well as the current supplements, handling of missing data for those that received risankizumab as non-responders may be a conservative approach; therefore, the non-responder imputation appears reasonable and is not expected to overestimate treatment effect. The results for each co-primary efficacy endpoint were statistically significant (p-values < 0.001).

Generally, there were no substantial differences in the treatment effect among subgroups (sex, age (<65, ≥65 years), race (White, Black, Asian, Other), and baseline sPGA severity); however, note that racial subgroups other than White were limited in number.

7.4.2. Conclusions and Recommendations

The applicant submitted results from a multicenter, randomized, double-blind, placebo-controlled study to assess the safety and efficacy of risankizumab using a new formulation (prefilled syringe 150 mg/mL), Trial M15-999 to support the approval of a new product presentation of 150 mg/mL SKYRIZI injection in prefilled syringe with needle-stick prevention device (PFS-NSP). The applicant also submitted results from an open-label, single-arm, usability study using a new autoinjector product presentation, 150 mg/mL SKYRIZI pen injection. The co-primary efficacy endpoints were the proportion of subjects achieving a sPGA score of 0 or 1, with at least 2-grade improvement from baseline, at Week 16, and the proportion of subjects achieving PASI 90 at Week 16.

In Trial M15-999, risankizumab was statistically superior to placebo (p-values <0.001) for both co-primary efficacy endpoints at Week 16. The applicant's reported results from their open-label Trial M16-005 showed similar responses for the co-primary endpoints of sPGA 0 or 1 and PASI 90 at Week 16.

8 Labeling Recommendations

8.1. Prescribing Information

Summary of Labeling changes

Section	Additional Comments
2 DOSAGE AND ADMINISTRATION	Language added to advise single dosing with the 150 mg/mL pre-filled syringe and 150 mg/ mL pen
12 CLINICAL PHARMACOLOGY	Labeling related to bioequivalence is added as discussed in section 6.2.3
16 HOW SUPPLIED	150 mg/mL pre-filled syringe and 150 mg/ mL pen presentations are added

The applicant did not propose additional labeling based on the clinical trials and the Division agrees that the data from the clinical trials do not warrant additional labeling.

8.2. Patient Labeling

The applicant submitted a Medication Guide (MG) and Instructions for Use (IFU) for risankizumab. The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) reviewed and provided comments on the submitted patient labeling. The final labeling will reflect their recommendations. Refer to the Patient Labeling Review by Morgan Walker, PharmD, MBA, CPH Laurie Buonaccorsi, PharmD (dated 3/10/2021).

9 Postmarketing Requirements and Commitments

CDRH has recommended the following PMC:

For your AutoInjector, you state that the user needs to be able to determine if the dose was administered successfully, and therefore designed your combination product to indicate by auditory means to the user, that the injection process is complete. However, there is no specific acceptance criteria or related after-assembly release testing for this audible feedback (click sound volume, timing, correlation with dose delivery) function of your device to ensure that the quality of this attribute as designed is effectively and reliability maintained. Your intended user may solely rely on the audible feedback to indicate end of injection, therefore either,

1. Implement and validate component inspection criteria specific to those design dimensions which are critical to maintain that the “hammers” of the control unit disengage at the stated fixed nomial distance relative to the end of the syringe barrel in order to achieve no more than 0.05mL at the time of the audible click. In addition, implement and validate component inspection criteria for those design dimensions which are responsible for the audible click volume.

Or

2. Implement and provide verification testing of design input requirements and assembly release testing for your audible click volume (i.e., decibels) and timing (+/- seconds from end of injection) or residual volume after click (delivered volume remaining in device after audible click.

10 Appendices

10.1. Financial Disclosure

In compliance with 21 CFR Part 54, the applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were Trials M15-990, M15-999, and M16-005.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified; M15-990: 18 M16-005:104 M15-999: 128		

Number of investigators who are sponsor employees (including both full-time and part-time employees): 12
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 19
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 19 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

None of the investigational sites enrolled a significant number of subjects that could potentially bias the clinical studies

11 Office Director (or designated signatory authority)

I concur with the approval recommendation of the review team and the post-marketing commitment requested by CDRH.

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/

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s009/010

PRODUCT QUALITY REVIEW (s)

PRODUCT QUALITY REVIEW

Date: April 8, 2021
To: Files for STN 761105/9 (SDN 419) and STN761105/10 (SDN 440)
From: Milos Dokmanovic, Ph.D., RAC, Product Quality Reviewer, DBRRI/OBP
Through: Riley Myers, Ph.D., Team Leader, DBRRI/OBP
Qing (Joanna) Zhou, Ph.D., Review Chief, DBRRI/OBP
Product: Risankizumab (Skyrizi ™)
Indication: Treatment of patients with moderate to severe plaque psoriasis
Sponsor: AbbVie, Inc.
Contact: Mary Konkowski, Director, Global Regulatory Strategy, US/Canada Lead
1 N. Waukegan Road
Dept. PA72/Bldg. AP30-4
North Chicago, IL60064

Received by FDA: June 26, 2020

Purpose of submission: Combined efficacy supplements 9/10: To introduce 150mg/mL drug substance (DS) and two new drug product (DP) presentations: 150mg/mL pre-filled syringe (PFS) with needle-stick prevention device (PFS-NSP) and 150mg/mL autoinjector (AI).

Action Due date: April 26, 2021

Review Recommendation: It is recommended that Supplements 9 and 10 be approved.

Background

Supplement 9 provides for the introduction of 150mg/mL pre-filled syringe (PFS) with needle stick protection device (NSP) and includes changes to the DS and PFS DP processes to enable manufacture of this new formulation. Additional changes include DS and PFS specifications to reflect changes in formulation, the use of new potency assay ((b) (4)) and new testing sites, updates to reference standard (RS) qualification protocol, changes in DS container closure system (CCS) and DS and PFS long-term storage conditions (storage temperature and shelf-life change for DS and shelf-life change for PFS). The following information and data were included in the submission to support the proposed changes: DS and PFS manufacturing process characterization (PCS) and process validation studies, formulation robustness, comparability assessment between 150mg/mL DS and PFS lots and commercial 90mg/mL DS and PFS lots, supplemental DS characterization and method validation data for all analytical procedure that are

impacted by the change in formulation, method validation and method transfer studies for the new RGA bioassay, extractables and leachables studies for CCS, evaluation of product quality upon NSP device assembly and solution extrusion, shipping qualification and simulated shipping studies, and immunogenicity assay validation data. Supplement 10 provides for the introduction of 150mg/mL autoinjector (AI) and includes a product quality assessment following device assembly, solution extrusion and shipping. Because clinical and product quality data to support the AI in supplement 10 are cross-referenced to supplement 9, it was decided that these supplements would be reviewed together. Therefore, this review includes supplements 9 and 10.

The intention behind introduction of 150mg/mL formulation in both presentations (PFS-NSP and AI) is to enable easier product administration (one instead of two injections); the dosing regimen (150 mg at weeks 0, 4 and every 12 weeks thereafter) and the route of administration (subcutaneous) will remain the same as approved for 90mg/mL PFS-NSP. The new DP presentations were evaluated in a Phase 1 study in healthy volunteers (bioavailability study M15-990) and Phase 3 study in patients with moderate to severe plaque psoriasis (studies M15-999 and M16-005).

Note:

1. ***Reviewer's comments are in italics.***
2. ***The pictures, graphs, and tables in this review are directly taken from the submission, unless otherwise noted.***
3. ***All information related to microbial control was deferred to OPMA. All information related to device function was deferred to CDRH.***
4. ***This review memo combines information from Supplements 9 and 10, because Supplement 10 includes product quality data after assembly of and extrusion through the autoinjector and cross references information for DS and PFS to Supplement 9.***

Supplement 9 (SDN 419)

3.2.S Drug Substance

3.2.S.1 General information

Risankizumab 150mg/mL DS is a colorless to yellow, clear to slightly opalescent solution formulated in 9.1mM sodium acetate, 0.9 mM acetic acid, 185mM trehalose dihydrate, and 0.2mg/mL polysorbate 20 (PS20) at pH 5.7.

(b) (4)

3.2.S.2 Manufacturer(s)

(b) (4)

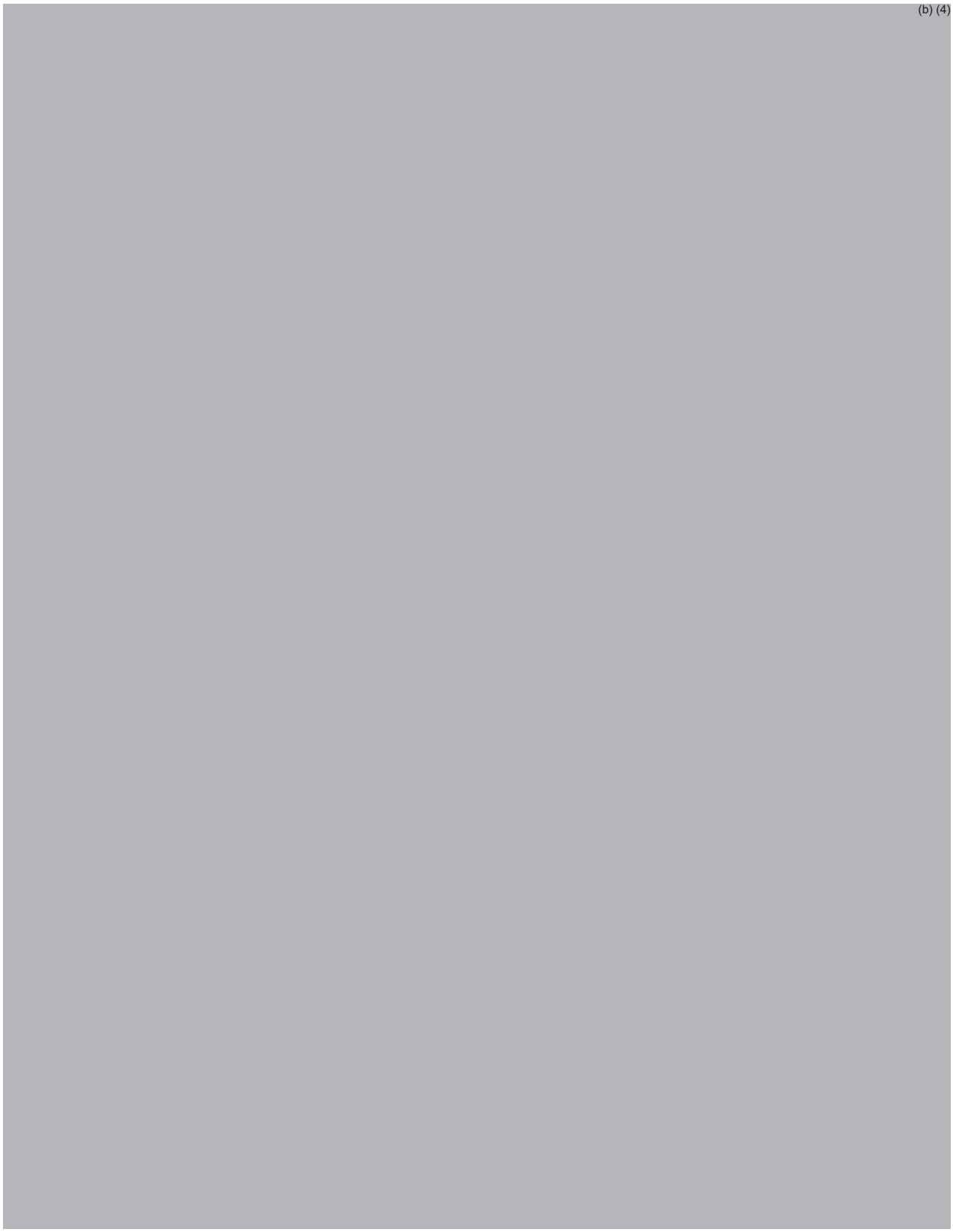
Reviewer comment: *All testing sites listed above are the same as used for 90mg/mL DS and are supported by the results from method validation and method transfer studies (reviewed in Section 3.2.S.4.3).*

3.2.S.2 Manufacture

3.2.S.2.2 Description of manufacturing process and process controls/3.2.S.2.4 Control of critical steps and intermediates

(b) (4)

Reviewer comment: *Acceptable ranges that are wider than those in the 90mg/mL process or newly introduced in the 150mg/mL process are in bold.*



(b) (4)

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(b) (4)

Conclusions:

I. Recommendation: I recommend approval of this supplement from a product quality perspective.

II. Sections Deferred to other reviewers: Review of microbial control in both supplements was deferred to OPMA and review of the device components (NSP and AI) was deferred to CDRH.

III. Post-marketing commitments: None

IV. Future Inspection Items: None

Milos Dokmanovic

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Riley C Myers

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Qing Zhou

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U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Pharmaceutical Manufacturing Assessment
Division of Biotechnology Manufacturing

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

Reviewer: Amy Devlin, Ph.D.
Secondary Reviewer: Maxwell Van Tassell, Ph.D.

BLA:	761105/9, 761105/10
Applicant:	AbbVie, Inc.
US License Number:	1889
Submission Reviewed:	PAS: (9): proposal of 150 mg/mL drug formulation and drug product presentation in a prefilled syringe with needle-stick prevention device; (10): proposal of autoinjector product presentation using formulation proposed in supplement 9
Product:	Skyrizi® (risankizumab-rzaa)
Indication:	moderate to severe plaque psoriasis
Dosage Form:	solution for s.c. injection, 150 mg/1.0 mL
Manufacturing Sites:	(b) (4) AbbVie Biotechnology Limited, Barceloneta, Puerto Rico (FEI: 3004620772)
FDA Receipt Date:	06/26/2020
Action Date:	04/26/2021

Conclusion and Approvability Recommendation

These prior approval supplements, as amended, were reviewed from a product quality microbiology and sterility assurance perspective and are recommended for approval.

Product Quality Microbiology Assessment

Product Quality Microbiology Information Reviewed

Sequence	Date	Description
eCTD 0074	06/26/2020	Prior approval supplement 9
eCTD 0079	07/27/2020	Prior approval supplement 10

Module 3.2

S DRUG SUBSTANCE [Risankizumab 150 mg/mL]

S.1 General Information

Risankizumab is a humanized immunoglobulin GI (IgG1) monoclonal antibody that selectively binds with high affinity to the p19 subunit of human interleukin 23 (IL-23) cytokine and inhibits interaction with the IL-23 receptor complex. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Risankizumab is manufactured using Chinese Hamster Ovary (CHO) cells. The formulated DS contains 150 mg/1.0 mL risankizumab at pH 5.7.

SATISFACTORY

S.2 Manufacture

(b) (4)

Table 1. List of Manufacturers provided in 3.2.S.2.1 of the submission.

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Conclusions

I. Prior approval supplements 9 and 10 were reviewed from a sterility assurance and product quality microbiology perspective and are recommended for approval.
II. Product quality aspects other than microbiology should be reviewed by OBP and CDRH.
III. Refer to Panorama for the cGMP status of the relevant facilities.

Amy Devlin

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Maxwell Van Tassell

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761105Orig1s009/10

OTHER REVIEW(S)

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	April 12, 2021
Assessor:	Jim Barlow RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Milos Dokmanovic PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	761105/S-010
Applicant:	AbbVie, Inc.
Submission Date:	July 27, 2020 (S-010)
Product:	SKYRIZI (risankizumab-rzaa)
Dosage form(s):	Injection
Strength and Container-Closure:	75 mg/0.83 mL in a single-dose prefilled syringe 150 mg/mL in a single-dosed prefilled Pen (proposed)
Purpose of assessment:	The Applicant submitted an efficacy supplement (S-010) for the purpose of this supplemental Biologics License Application (sBLA) to request FDA approval of a new autoinjector (AI) product presentation, 150 mg/mL SKYRIZI® Pen (risankizumab-rzaa) injection (referred to as the 150 mg/mL AI). The 150 mg/mL AI presentation uses the risankizumab 150 mg/mL formulation submitted in the June 26, 2020 BLA 761105 efficacy supplement (eCTD Sequence No. 0074). With the 150 mg/mL AI presentation, the dosing regimen and route of administration remain unchanged as 150 mg risankizumab administered by subcutaneous (SC) injection at Week 0, Week 4, and every 12 weeks thereafter. The 150 mg/mL AI presentation provides patients with the benefit of a single injection using an autoinjector instead of the 2 injections required with the current marketed 75 mg/0.83 mL prefilled syringes to achieve each 150 mg dose.
Recommendations:	The prescribing information, medication guide and instructions for use (submitted April 7, 2021), container labels (submitted on July 27, 2020) and carton labeling submitted on (submitted on March 19, 2021) are **acceptable** from an OBP labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The prescribing information, medication guide and instructions for use (submitted April 7, 2021), container labels (submitted on July 27, 2020) and carton labeling submitted on (submitted on March 19, 2021) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on July 27, 2020)
  \\CDSESUB1\evsprod\bla761105\0079\m1\us\114-labeling\draft\labeling\local-lbl-4351.docx

- Medication Guide (submitted on July 27, 2020)
  \\CDSESUB1\evsprod\bla761105\0079\m1\us\114-labeling\draft\labeling\local-lbl-4351.docx

- Instructions for Use (submitted on July 27, 2020)
  \\CDSESUB1\evsprod\bla761105\0079\m1\us\114-labeling\draft\labeling\local-lbl-4351.docx

- Container Labels 1 mL PEN front panel (submitted on July 27, 2020) (S-010)

(b) (4)

[redacted]

- Container Labels SAMPLE 1 mL PEN front panel (submitted on July 27, 2020) (S-010)

(b) (4)

[redacted]

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Acceptable

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Considered a partial label. Acceptable

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Considered a partial label so acceptable not to have this on the container.

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

NDC numbers **(container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**

Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Partial label so not needed. Acceptable.

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	Acceptable
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Expiration date (package labeling)	Acceptable
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	Acceptable
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	Acceptable
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Per 21 CFR 610.61(e) the statement "Contains no preservatives" is listed on the carton label.

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

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i) (i) The words "Shake Well", "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product;	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	Acceptable
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To QR: Does this device contain any natural rubber?

RESPONSE: It is confirmed that the plunger stopper is latex-free and the AI has no product contacting surfaces.

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revise inactive ingredient components of the ingredient statement to appear in alphabetical order per Labeling of Inactive Ingredients, USP General Chapters <7> Labeling.

RESPONSE: Applicant revised as requested.

Source of the product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	Acceptable
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: "No US standard of Potency" statement is located on the carton per 21 CFR 601.61(r). Acceptable

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize	✓ Yes ☐ No

Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendatio
Please confirm there is sufficient white space surrounding the linear barcode. The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

RESPONSE: Applicant revised to provide more white space.

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☐ Yes ☐ No

	☒ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	**Acceptable**

Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant comment: Revise the statement appearing at the top of the Principal Display Panel (PDP) from "Prefilled Single-Dose Pen" to read "One 1 mL Single-Dose Prefilled Pen" to include the net quantity statement, as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013

RESPONSE: Applicant revised as requested

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Med Guide Statement is listed on carton. Acceptable

Other (package labeling)	**Acceptable**
	☐ Yes ☐ No ☒ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g.,	✓ Yes ☐ No ☐ N/A

tubing, infusion aids, or filter membranes) incompatibilities with these components	

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Added the identifying characteristics of the dosage form.
The Applicant revised as requested

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Added the molecular weight 146 kDa. *The Applicant revised as requested*
Revised inactive ingredients to appear in alphabetical order consistent with the 75 mg/0.83 mL presentation *The Applicant revised as requested*
Provided the pH *The Applicant revised as requested*

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*	☐ Yes ☐ No ☒ N/A

Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Patient Information Labeling Evaluation

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

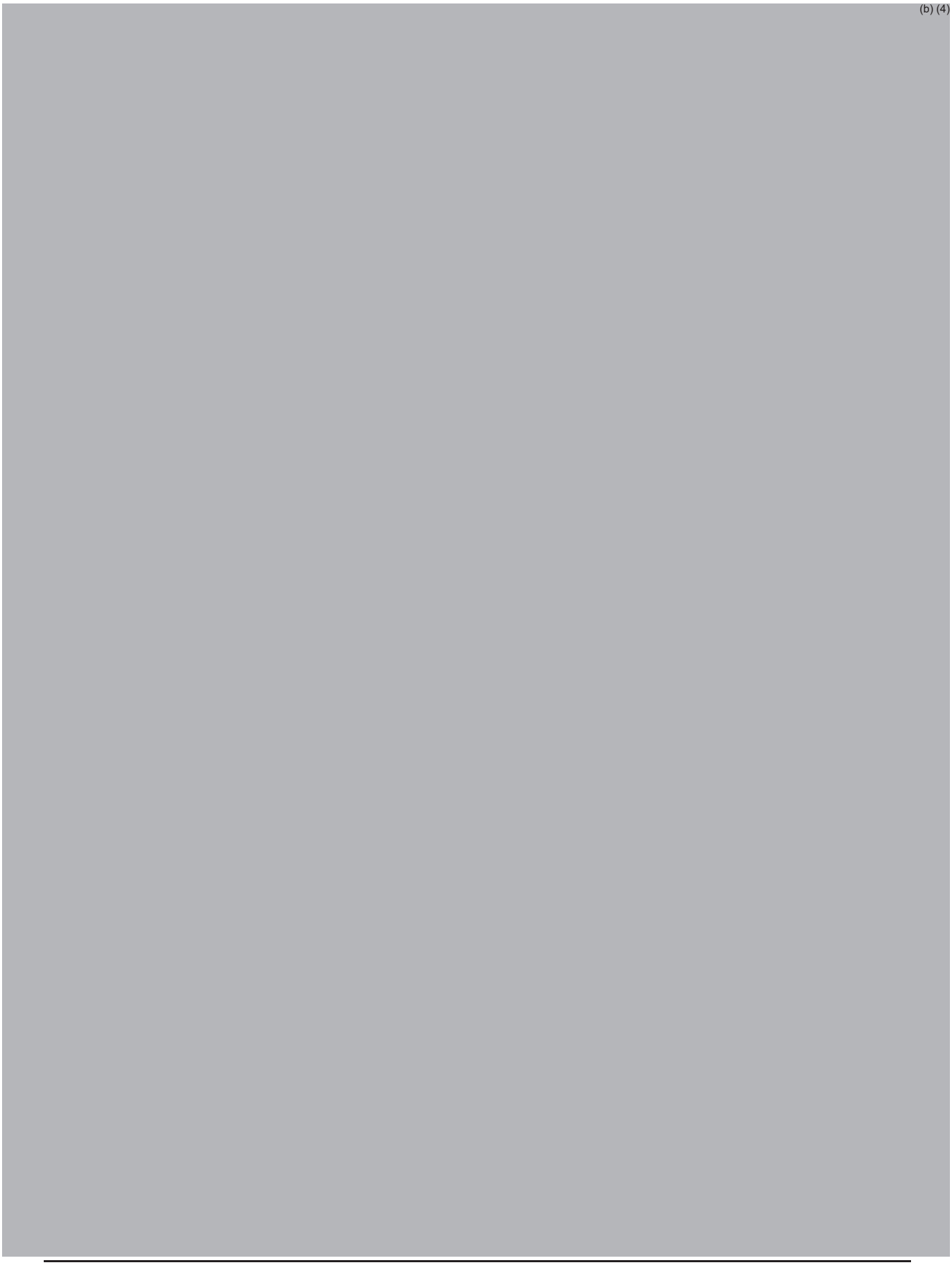
INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *21 CFR 610.61 (add the US license number for consistency with the carton labeling),* *21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)*	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information, Medication Guide/Instructions for Use (submitted on April 7, 2021)
  \\CDSESUB1\evsprod\bla761105\0118\m1\us\114-labeling\draft\labeling\local-lbl-4351.docx

- Container Labels for Marketed and Sample (submitted on July 27, 2020)

(b) (4)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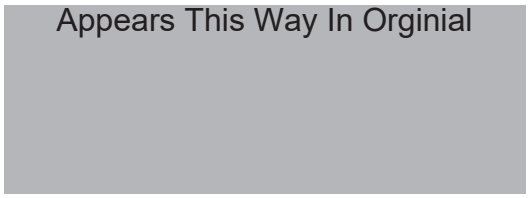
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Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	April 12, 2021
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Milos Dokmanovi, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761105/S-009
Applicant:	AbbVie, Inc.
Submission Date:	June 26, 2020
Product:	Skyrizi (risankizumab-rzaa)
Dosage form(s):	injection
Strength and Container-Closure:	75 mg/0.83 mL in a single-dose prefilled syringe 150 mg/mL in a single-dose prefilled syringe (proposed)
Purpose of assessment:	The Applicant submitted an efficacy supplement to propose a 150 mg/mL in a single-dose prefilled syringe for Agency assessment.
Recommendations:	The prescribing information, medication guide and instructions for use (submitted on April 7, 2021), container labels (submitted on June 26, 2020), and carton labeling (submitted on March 19, 2021) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

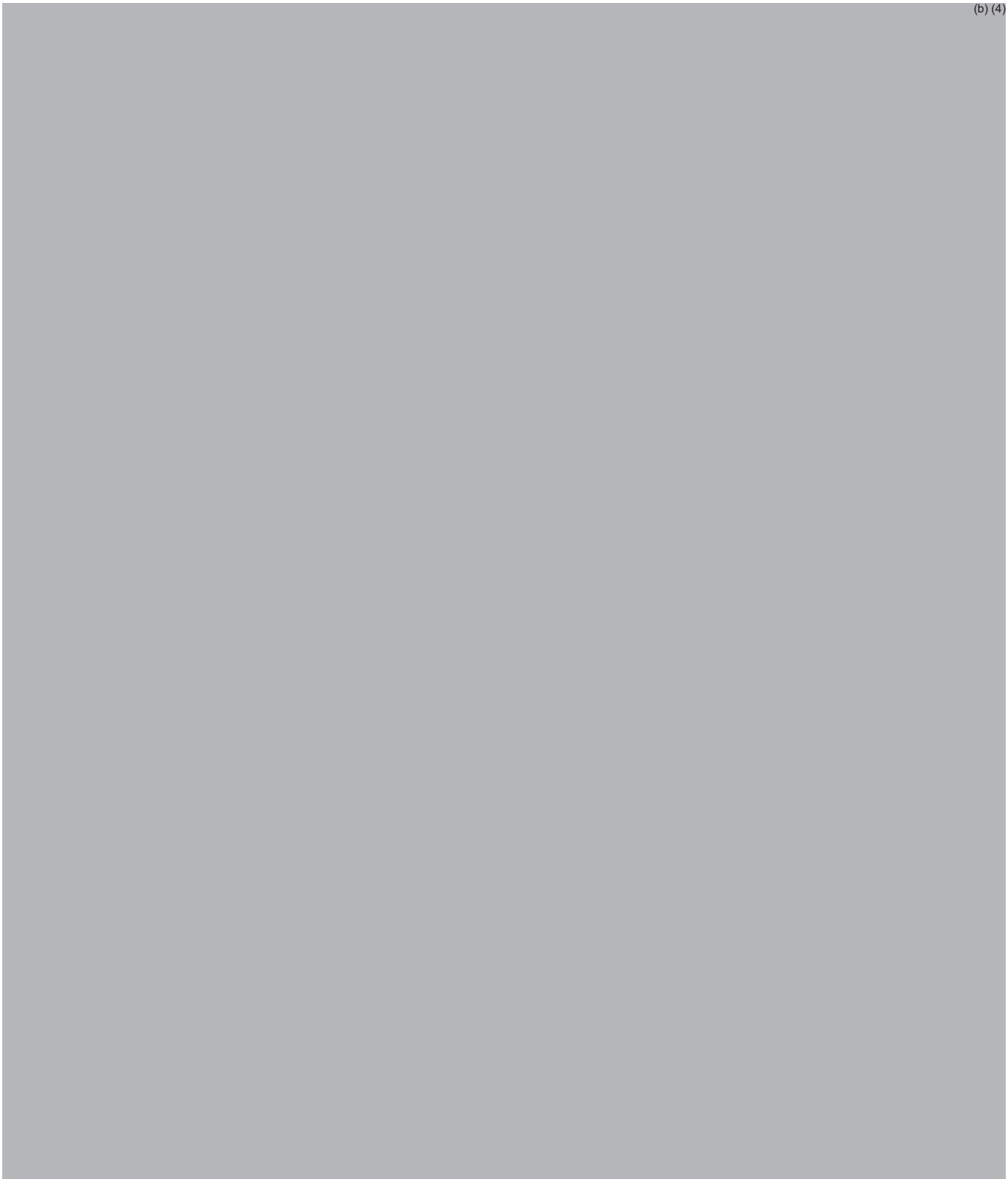
The prescribing information, medication guide and instructions for use (submitted on April 7, 2021), container labels (submitted on June 26, 2020), and carton labeling (submitted on March 19, 2021) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide/Instructions for Use (submitted on October 15, 2020 \\CDSESUB1\evsprod\bla761105\0088\m1\us\114-labeling\draft\labeling\local-lbl-4351.docx)

(b) (4)


(b) (4)


(b) (4)

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	☐ Yes ☐ No ☒ N/A

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

NDC numbers **(container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	☐ Yes ☐ No ☒ N/A

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	☐ Yes ☐ No ☒ N/A

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

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

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise inactive ingredient components of the ingredient statement to appear in alphabetical order
The Applicant revised as requested

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Spanish-language (Drugs) (package labeling)	Acceptable
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	Acceptable
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Phenylalanine as a component of aspartame (package labeling)	Acceptable
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Sulfites; required warning statements (package labeling)	Acceptable
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Statement of Dosage (package labeling)	Acceptable
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Dispensing container (package labeling)	Acceptable
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Medication Guide (package labeling)	Acceptable
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	✓ Yes ☐ No ☐ N/A

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	☐ Yes ☐ No ☒ N/A

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Added the identifying characteristics of the dosage form
The Applicant revised as requested

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Added the molecular weight 146 kDa. *The Applicant revised as requested*
Relocated the container closure information to how supplied section since it includes important information about the difference in needle gauge between the two PFS presentations *The Applicant revised as requested*
Revised inactive ingredients to appear in alphabetical order consistent with the 75 mg/0.83 mL presentation *The Applicant revised as requested*
Provided the pH *The Applicant revised as requested*

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Added identifying characteristics. *The Applicant revised as requested* Revised the table for readability *The Applicant revised as requested* Relocated the needle gauge and size from section 11 to section 16 *The Applicant revised as requested*

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Medication Guide Evaluation

MEDICATION GUIDE	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(7)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
STORAGE AND HANDLING	**Acceptable**
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Patient Information Labeling Evaluation (N/A)

Instructions for Use Evaluation

INSTRUCTIONS FOR USE	
TITLE (NAMES AND DOSAGE FORM)	
Recommended Labeling Practices references: Proprietary name in upper case letters on line 1, proper name (line 2) in lower case letters in parentheses, and dosage form followed by the route of administration (line 3) in lower case letters (see Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for IFU: Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

INSTRUCTIONS FOR USE	
INGREDIENTS	**Acceptable**
Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	☐ Yes ☐ No ☒ N/A

INSTRUCTIONS FOR USE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
Draft Instructions for Use – Patient Labeling for Human Prescription Drug and Biological products and Drug-Device and Biologic-Device Combination Products – Content and Format Guidance for Industry (July 2019). *21 CFR 610.61 (add the US license number for consistency with the carton labeling),* *21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)*	✓ Yes ☐ No ☐ N/A

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information/Medication Guide/Instructions for Use (submitted on April 7, 2021 \\CDSESUB1\evsprod\bla761105\0118\m1\us\114-labeling\draft\labeling\local-lbl-4351.pdf)

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Milos Dokmanovic

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

PATIENT LABELING REVIEW

Date:	March 10, 2021
To:	Craig Johnson, PharmD Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD **Regulatory Review Officer** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	SKYRIZI (risankizumab-rzaa)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761105
Supplement Number:	S-009 and S-010
Applicant:	AbbVie, Inc.

1 INTRODUCTION

On June 26, 2020 and July 27, 2020, AbbVie, Inc. submitted for the Agency's review a Prior Approval Labeling Supplement to their Biologics License Application (BLA) 761105 S-009 and S-010 for SKYRIZI (risankizumab-rzaa) injection. Supplement 009 provides a proposed new 150 mg/mL prefilled syringe presentation and Supplement 010 provides a proposed new 150 mg/mL autoinjector presentation. The 150 mg/mL product presentations provide patients with the benefit of a single injection instead of 2 injections to achieve each 150 mg dose.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Dermatology and Dentistry (DDD) on August 19, 2020 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for SKYRIZI (risankizumab-rzaa) injection.

2 MATERIAL REVIEWED

- Draft SKYRIZI (risankizumab-rzaa) injection MG and IFU received on June 26, 2020, July 27, 2020, and received by DMPP and OPDP on February 26, 2021
- Draft SKYRIZI (risankizumab-rzaa) injection Prescribing Information (PI) received on July 27, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 26, 2021.

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%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and PPI are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.


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HUMAN FACTORS RESULTS AND LABELS AND LABELING REVIEW

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

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

Date of This Review:	January 15, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761105/S-009
Product Type:	Combination Product
Drug Constituent Name and Strength	Skyrizi (risankizumab -rzaa) injection 150 mg/mL
Device Constituent:	Pre-filled Syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	AbbVie, Inc. (AbbVie)
Submission Date:	June 26, 2020
OSE RCM #:	2020-1366 (BLA 761105/ S-009)
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting):	Jason Flint, MBA, PMP
DMEPA Associate Director of Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761105 Supplement 9 for Skyrizi (risankizumab-rzaa) injection. This is a combination product with a proposed pre-filled syringe (PFS) device constituent part that is intended to treat moderate-to-severe plaque psoriasis in adults. The Applicant is seeking licensure for the 150 mg/mL strength in a single-dose PFS.

1.1. PRODUCT DESCRIPTION

Skyrizi (risankizumab-rzaa) was approved under BLA 761105 on April 23, 2019 and is currently available as a PFS in 75 mg/0.83 mL strength. The recommended dose is 150 mg, which currently requires 2x 75 mg injections administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.

The proposed device user interface is comprised of a package carton with Quick Tips (QT) containing one 150 mg/mL PFS with Needle Stick Protection (NSP) in a cardboard sleeve, one set of instructions for use (IFU), and one package insert (PI) containing a Medication Guide. Skyrizi is intended for administration by patients and healthcare providers (HCPs) in the home or healthcare setting.

1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

AbbVie, Inc. submitted a HF validation study protocol under IND 113306 on June 29, 2017 and (b) (4) on July 5, 2017. We identified deficiencies in the protocols and

communicated the deficiencies to the sponsor on September 22, 2017[1] and November 28, 2017[2]. We reviewed AbbVie's HF validation study results report to support BLA 761105 and found the results were adequate from a medication error perspective.[3]

AbbVie submitted the results of an HF validation study under BLA 761105/S-001[4], to support design changes to the currently approved user interface.[5] We found the proposed product acceptable from a medication error perspective.

Additionally, we reviewed the use-related risk analysis (URRA)[6] for the proposed product. Based on our review of the URRA, we determined that AbbVie does not need to submit the results of the HF validation study as part of the BLA to support the product user interface for the moderate to severe plaque psoriasis indication. However, if the product user interface is modified prior to the approval of the marketing application, additional human factors considerations may apply.

On June 26, 2020, AbbVie submitted their prior approval supplement (BLA 751105/S-009) for the 150 mg/mL PFS with results from a supplemental human factors validation study, which is the subject of this review. In their submission, AbbVie notes that upon approval of the 150 mg/mL risankizumab-rzaa PFS, AbbVie will cease production of the 75 mg/0.83 mL (90 mg/mL) risankizumab-rzaa. AbbVie will submit a prior approval labeling supplement approximately 6 months prior to the expiration of the last lot of the 75 mg/0.83 mL PFS-NSP in order to request approval of labeling that is specific to the 150 mg/mL PFS-NSP only.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review

[1] Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 22. RCM No.: 2017-1294 and 2017-1719.

[2] Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 27. RCM No.: 2017-1719-1.

[3] Patel, M. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 22. RCM No.: 2018-886 and 2018-910.

[4] The sponsor referred to this submission as a supplemental study because they pooled data from the results of the HF validation study in the original BLA submission.

[5] Schlick, J. Human Factor Results and Label –Labeling Review for risankizumab BLA 761105/S-01. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 01. RCM No.: 2019-935 and 2019-1029.

[6] Schlick, J. Use-related Risk Analysis Review for Skyrizi (risankizumab-rzaa) (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019AUG01. RCM No.: 2019-1199.

Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design (Table 2), errors/close calls/use difficulties observed (Table 3), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The HF validation study was conducted with three representative user groups, and no training was offered. Table 2 shows representative user groups and sample sizes.

Table 2. User groups and sample sizes

User Group	**Sample Size**
Patients [Plaque Psoriasis (PsO), Psoriatic Arthritis (PsA)]	15
Caregivers	15
Healthcare Professionals	15

The HF validation study was conducted in an environment similar to either a home or clinical environment. Moderators were present to observe, but did not intervene while participants were conducting the simulated use scenario.

Per the Applicant, the critical task from the initial validation that is relevant and the focus of this supplemental study is: *Slowly push the plunger all the way in until all the liquid injected and the syringe is empty.*

3.2 RESULTS AND ANALYSES

Table 3 describes the study results, the Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Push the plunger in all the way until all medication is administered (C)	**n=8** (b) (6) (b) (6) pulled out plunger. (b) (6) pulled it back before removing the needle cover. (b) (6) pulled it out while removing the needle cover. (b) (6) did not remove the needle cover before injecting. (b) (6) also did not remove the syringe sleeve.	0	(b) said, "I overprepared it (the syringe) and I pulled and the plunger came off. "I didn't know where to hold it. I wasn't sure how to pull back" Has seen HCPs administer allergy shots the same way. (b) said she wasn't sure what to do to remove the needle cover; stated she had looked a picture and text in IFU but wasn't sure of purpose of (finger grips) in Step 4. Also said plunger came out very easily and was	*Cognition > Mental Model* (b) (6) ssumed that it needed to be pulled back similar to drawing a syringe from a vial of medication. Was injection naïve and had only ever seen vial syringes used by his health care provider. *Perception > Insufficiently Prominent Guidance* (b) (6) did not understand from the IFU which part of the device was meant by the 'needle cover' or how to hold the device in order to remove the cover. As a result, she	Proposing two modifications to the IFU based on two participants (b) (6) (b) (6) pulling plunger out of the syringe and one participant (b) (6) not removing the carboard sleeve and attempted to inject with both the sleeve and needle cover still in place. (b) (6) Placing the removed plunger back into the device potentially results in contamination of the stopper, injection of a low pathogen load and the risk of localized infection requiring medical intervention as standard of care. The participant mentioned that he "overprepared" the	We note the potential harm associated with use errors resulting in a loss of drug product is the risk of delayed administration, wrong dose errors, and suboptimal treatment which could lead to flare up of the disease state. We acknowledge the Applicant's proposed mitigation strategy to mitigate the risk of users pulling on the plunger when removing the PFS from the sleeve or when removing the needle cover with the

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	(b) (6) primed the syringe. (b) (6) epressed the plunger until could no longer see liquid but NSP did not engage. (b) (6) held thumb on plunger. C07 held thumb on the plunger after uncapping while reading IFU (b) (6) held thumb on plunger while uncapping.		concerned how easy it was to pull out. (b) (6) aid she thinks she did it wrong, but didn't think it was difficult and instructions were very straightforward and simple, just thinks it was her error maybe from inexperience; was confused by the cardboard sleeve and wasn't sure if she was supposed to take it off or not; wasn't sure if the cardboard was part of the packaging or if it	gripped the device by both ends and pulled when she read in the IFU to remove the needle cover. (b) (6) attempted to complete the injection with the sleeve still covering the syringe, having not seen any information in the materials stating that the syringe sleeve must be removed prior to use. There was no information on the syringe sleeve nor in the IFU stating that the sleeve must be removed prior to use.	syringe thus indicating he recognized the error. As a result, it is likely this error would only have occurred on the first injection attempt and this does not represent an ongoing pattern of use error. (b) (6) Removing the plunger from the device and the resulting loss of drug makes the device unusable resulting in delayed administration until the dose is replaced. The potential harm associated with this use error is flare up of the disease state that may require additional treatment. The participant noticed her error and she would change her behavior and	addition of the statements "**Do not** hold or pull plunger rod when removing the prefilled syringe from the sleeve." under Step 1 (Gather the supplies for the injection) and (b) (4) (b) (4) We find the addition of these statements may further mitigate this use error. Thus, we find the residual risk is acceptable and have no

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			was supposed to provide more of a grip to help hold the syringe; expected removal instructions would be included either in IFU or on the syringe sleeve. (b) (6) hought she had read "Do not remove the cap" in the IFU, pointed to Step 3 "oh…it says to pull off the cap. I thought it says don't pull off the cap. I associated 'DO NOT' here [last line of red text for Step 3 in the IFU] with [the image of] the needle cap. Oh I did not see Step 4 at all.	(b) (6) hile reviewing the IFU and reading instructions for Step 3 and 4 in the IFU, the Participant associated the instruction beginning 'DO NOT' with the diagram and missed the instructions in Step 4 describing removal of the needle cover, leading to her to believe she should not pull off the needle cover before administering the injection. *Cognition > Negative Transfer*	avoid pulling the plunger during future injections. As a result, it is likely this error would only have occurred on the first injection attempt and this does not represent an ongoing pattern of use error. (b) (6) erforming an injection without removing the syringe sleeve and needle cover results in delayed administration until the dose is replaced. The potential harm associated with this use error is flare up of the disease state that may require additional treatment. The participant noticed her error and it can be inferred she would	further recommendations at this time. In this instance, we determined the additional statements to the IFU do not warrant submission of additional HF validation study data. . To mitigate the risk of users not removing the cardboard sleeve, the Applicant added the following to (b) (4) of the IFU: "Remove prefilled syringe from cardboard sleeve by holding the finger grip."

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			When asked for more detail, stated "I was reading this [Step 3] and reading "DO NOT" and seeing the picture, I just figured I knew how to do it." (b) (6) explained "A lot of syringes that you normally use in practice or in a hospital, you wouldn't see that much dripping. Seemed like a lot of dripping." He was then asked why he primed the syringe and stated that he was inspecting the medication and	(b) (6) The participant assumed this syringe worked similarly to other syringes he'd used in clinical practice, which required priming before injection. Participant did not look at the provided instructional materials at all. (b) (6) ased on this participant's experience with a range of syringe-injected medications, she anticipated and responded to perceived haptic and auditory feedback that the plunger was fully depressed and the dose had been fully administered.	change her behavior and remove the sleeve for future injections. As a result, it is likely this error would only have occurred on the first injection attempt and this does not represent an ongoing pattern of use error. (b) (6) Performing an ction without removing the needle cover results in delayed administration until the dose is replaced. The potential harm associated with this use error is flare up of the disease state that may require additional treatment. The use of an injection pad makes it difficult to determine whether or not this would represent	Per the Applicant's subsequent response to our information request (IR) (See Appendix E), the cardboard sleeve holds the PFS in place within the carton and the Applicant is not proposing any additional mitigation strategies to address the use errors. Per the Applicant, it is not likely that the use error would be repeated or lead to a pattern detrimental to treatment. We note the IFU and QT do not identify/label the cardboard sleeve and no

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			looking to eliminate any bubbles. When asked why instructions were not used, he replied, "These [syringes] work basically the same way. With a new drug I might give it a quick look […] We are usually made aware [of those differences] from other people (colleagues and drug reps) so we (physicians) don't need to read that." (b) (6) depressed the plunger until she felt and heard it hit the bottom of	*Cognition > Device Design* (b) (6) he participant held her thumb on the plunger after uncapping the device because the design of the device suggested that it should be held in this way. NOTE: the design of the syringe, which suggested the hand position used by the participant, is not unique to this PFS with NSP and is common across most syringes with flanges currently available on the market.	a pattern of use error since the participant had no feedback from an actual patient that a needle stick did not occur. That type of feedback could indicate to the participant that an error was made. Without that feedback a pattern of use error cannot be ruled out in this circumstance. (b) (6) he amount of product lost to wet injection from the PFS is unlikely to affect the efficacy of treatment for PsO/PsA. This is a level below which it is currently understood there is no compromised medical therapy. Continued loss of this amount of drug	instructions were added to the cardboard sleeve itself or the QT. Additionally, our review of the samples identified 1) the proposed white cardboard sleeve blends in with the white finger flange of the syringe, making it difficult to distinguish from the PFS and 2) there is an opening at the needle cap end of the cardboard sleeve, which could lead to medication errors where users may not realize the cardboard

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			the barrel. She withdrew the needle from the injection pad and explained she doesn't like to continue to push the plunger down if she feels the injection is complete and all the injection has been administered. (b) (6) Placed thumb on plunger when picking up the device because it "felt natural", explaining, "there was a depression there, and that's just intuitive – to put the long part between your two	*Perception > Insufficiently Prominent Guidance* (b) (6) The participant held her thumb on the plunger while uncapping the device, and the pressure of her thumb on the plunger resulted in a small arc of medication to squirt out of the syringe. The participant held the syringe this way because she looked at the written instructions and did not initially notice the picture.	product through a pattern of wet injections is also of minimal clinical significance, not classified as compromised medical therapy and does not indicate potential harm.	sleeve needs to be removed prior to injection. Therefore, based on our review of the product samples, IFU, QT, participants' subjective feedback, and root cause analysis, we provide recommendations to the carton labeling, cardboard sleeve, QT, and IFU to further emphasize removing the cardboard sleeve prior to injection. In this instance, we determined the changes do not warrant submission of additional

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			fingers and thumb on the plunger", device was "ergonomically designed". (b) stated had difficulty removing the needle cover and she's not used to syringes "spraying like that", "maybe I took it off too strongly; when asked what in the IFU led her to hold the device with her thumb on the plunger she said "I guess I was just busy reading [the instructions] first, before looking at [the picture]. And I was just…trying			human factors validation study data. See Section 4.1 for our recommendations.. The Applicant proposes no mitigation for the following errors that could result in loss of drug product: not removing the needle cover, placing thumb on the plunger before ready to inject, priming the syringe, not pressing down the plunger until the NSP is engaged. Our review of the IFU determines that Step 4

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			to gently pull the needle cover straight off…I didn't think it came off very easily, so I used more force."			of the IFU and Step 2 of the Quick Tips provide instructions and both are accompanied by images of removing the needle cover. We also determined Step 5 of the IFU provides instructions to hold the body of the prefilled syringe in one hand between the thumb and index fingers. We find the image and text in Step 6 of the IFU provides the important information needed to successfully perform the task of pushing down on the plunger rod and

Table 3: Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and E for Essential)	**Number of Use Errors and Description of Use Errors**	**Number of Close Calls and Use Difficulties and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
						activating the NSP step of the injection process. We find the IFU statements and images mitigate these use errors to the extent possible. Thus, we find the residual risk is acceptable and we have no recommendations at this time.

ANALYSIS OF OTHER CRITICAL TASKS AND NON-CRITICAL TASKS

Per Applicant, in the initial validation, there were four critical tasks identified to successfully administer a full dose using the PFS with NSP. Two of these critical tasks (select injection site and remove the needle cover) were validated in the initial HF validation study and are out of scope for this supplemental study. The critical task of administering the second injection from the initial validation is no longer relevant with the proposed 150 mg strength PFS. The critical task from the initial validation that is relevant and the focus of this supplemental test is: *Slowly push the plunger all the way in*

until all the liquid is injected and the syringe is empty.

The supplemental HF validation study identified a use error with the other critical task of: *Select Injection Site*. n=1 participant was observed administering the simulated injection into their forearm. The Applicant proposes no mitigation strategies. Our review of the IFU and QT determines that Step 2 of the IFU and Step 1 of the QT provide instructions and both are accompanied by images of injectable areas. We find the IFU and QT statements and images mitigate this use error to the extent possible. Thus, we find the residual risk acceptable and we have no recommendations at this time.

The supplemental HF validation study identified use errors with the following essential task: *Medication Inspection*. n = 14 participants did not appear to inspect the solution prior to administering the simulated injection. The Applicant proposes no mitigation strategies.

Per Applicant, one participant was also observed twisting the needle cover when attempting to remove, which resulted in the needle cover breaking during removal, leaving part of the needle cover on the needle. The session was paused to replace the defective device with a new syringe. No root cause probing was conducted during the session, as this situation was not identified as a failure in the moment. It was assumed that the device was defecting, resulting in a Product Complaint being filed for compliance reasons. We provide our analysis of errors related to not removing the needle cover and our review of the IFU and QT in Table 2 above.

Per Applicant's IR response, the supplement study did not include root cause analysis for any other use errors observed beyond those associated with the critical task of: *Slowly push the plunger all the way in until all the liquid is injected and the syringe is empty*. The supplemental study was performed to confirm that the IFU changes associated with the change from two to one prefilled syringe did not introduce additional use-related risk. For the remaining critical tasks, AbbVie is relying upon the initial HF validation study that we previously reviewed. We note these other use errors were also observed in the HF validation study for the 75 mg/ 0.83 mL PFS where we concluded that the human factors validation study results are adequate from a medication error perspective.

3.4. LABELS AND LABELING

Table 4 below includes the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. We reviewed the Prescribing Information (PI) and found the PI acceptable from a medication error perspective.

Table 4: Identified Issues and Recommendations for AbbVie, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU)			
1.	Based on the use error of failing to remove the cardboard sleeve from the prefilled syringe (PFS) prior to injection, the participant's subjective feedback, and our review of the samples, the cardboard sleeve is difficult to distinguish from the PFS because (b) (6) (b) (6)	The potential harm associated with failure to remove the cardboard sleeve from the prefilled syringe prior to injection includes delay in therapy, loss of drug product, and underdose, which may result in flare of plaque psoriasis that may require additional treatment.	Consider adding a figure in beginning of the IFU with the cardboard sleeve labeled and showing the PFS in the cardboard sleeve. Additionally, consider adding a figure associated with Step 1 depicting the user removing the PFS from the cardboard sleeve.

	(b) (6)		
Carton Labeling			
1.	The net quantity statement does not appear on the principal display panel.	The net quantity statement should appear on the principal display panel (PDP), but should be separated from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).[7]	Revise the statement appearing at the top of the Principal Display Panel (PDP) from "Single-dose Prefilled Syringe" to read "One 1 mL Single-Dose Prefilled Syringe" to include the net quantity statement, as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013
2.	It is unclear if there is enough white space surrounding the linear barcode on the carton labeling.	Lack of sufficient white space surrounding the linear barcode could make it difficult for scanners to reach the barcode correctly.	Please confirm there is sufficient white space surrounding the linear barcode. The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).
3.	Based on the use error of failing to remove the cardboard sleeve from the prefilled syringe (PFS) prior to injection, the participant's subjective feedback, and our review of the samples, the cardboard sleeve is	The potential harm associated with failure to remove the cardboard sleeve from the prefilled syringe prior to injection includes delay in therapy, loss of drug product, and underdose, which may result in	Consider adding instructions or a note under Step 2 in the QT on removing the cardboard cover.

[7] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 461-463). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

	difficult to distinguish from the PFS because (b) (6) [redacted] (b) (6)	flare of plaque psoriasis that may require additional treatment.	
Packaging-Cardboard Sleeve			
1.	Based on the use error of failing to remove the cardboard sleeve from the prefilled syringe (PFS) prior to injection, the participant's subjective feedback, and our review of the samples, the cardboard sleeve is difficult to distinguish from the PFS because (b) (6) [redacted] (b) (6)	The potential harm associated with failure to remove the cardboard sleeve from the prefilled syringe prior to injection includes delay in therapy, loss of drug product, and underdose, which may result in flare of plaque psoriasis that may require additional treatment.	We recommend additional mitigation strategies (e.g. different color cardboard sleeve, adding a statement on the cardboard sleeve such as 'remove this cardboard sleeve prior to use', etc.)

	(b) (6)		

4. CONCLUSION AND RECOMMENDATIONS

The results of the supplemental HF validation study demonstrated several use errors with critical tasks that may result in harm to the patient. The Applicant proposes two revisions to the IFU based on the user errors seen with pulling on the plunger and not removing the cardboard sleeve from the PFS prior to injection. To mitigate the risk of users pulling on the plunger when removing the PFS from the sleeve or when removing the needle cover, the Applicant added statements under Steps 1 (b) (4) cautioning against holding or pulling on the plunger when performing those tasks. We find the addition of these statements minimize the residual risk to the extent possible. To mitigate the risk of users not removing the cardboard sleeve from the PFS prior to injection, the Applicant added additional instructions in Step (b) (4) of the IFU to remove the cardboard sleeve while gathering supplies. Per Applicant's subsequent response to our IR, they are not proposing any additional mitigation strategies. After reviewing the product samples, HF validation study results, participant's subjective feedback, and root cause analysis, we provide recommendations to the carton labeling, cardboard sleeve, QT, and IFU to further emphasize importance of removing the cardboard sleeve. See Section 4.1 for our recommendations.

The Applicant did not propose any revisions to the product user interface to mitigate the risk for the other use errors (e.g. not removing the needle cover, placing thumb on plunger before ready to inject, priming the syringe, not pressing down the plunger until the NSP is engaged). We note these other use errors were also observed in the HF validation study for the 75 mg/ 0.83 mL PFS where we concluded that the human factors validation study results are adequate from a medication error perspective. We acknowledge that some residual risks remain, but determined that based on our review of the IFU, QT, the subjective feedback and root cause analysis provided in the supplemental human factors validation study, the implementation of additional labeling mitigations are not likely to further reduce the residual risks.

Furthermore, our evaluation of the proposed user interface, proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the Applicant. In addition, we provide our recommendations for the Applicant related to the HF validation study in section 4.1 below. We recommend that the Applicant consider additional modifications to the user interface, and implement our recommendations. In this instance, we determined the changes do not warrant submission of additional human factors validation study data.

4.1 RECOMMENDATIONS FOR ABBVIE, INC.

Taking into account the human factors (HF) validation study results, subjective feedback, root cause analysis, and product samples, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations prior to approval of this supplement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Skyrizi that AbbVie, Inc. submitted on June 26, 2020.

Table 5. Relevant Product Information	
Initial Approval Date	April 23, 2019
Therapeutic Drug Class or New Drug Class	interleukin-23 antagonist, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody.
Active Ingredient (Drug or Biologic)	risankizumab-rzaa
Indication	treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.
Route of Administration	subcutaneous
Dosage Form	injection
Strength	Currently Approved: 75 mg/0.83 mL (90 mg/mL) Proposed: 150 mg/mL
Dose and Frequency	Currently approved: 150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. Proposed: 150 mg (one 150 mg injection) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.
How Supplied	Currently approved: Carton of two 75 mg/0.83 mL (90 mg/mL) in a single-dose prefilled syringe Proposed: Carton of one 150 mg/mL in a single dose pre-filled syringe
Storage	Store in a refrigerator at 2° C to 8° C (36° F to 46° F)
Container Closure/Device Constituent	Currently approved: Carton containing 2 prefilled syringes and 2 alcohol pads. Each prefilled syringe contains a 1 mL glass syringe with a fixed 29 gauge ½ inch needle with needle guard. Proposed: Carton containing 1 prefilled syringe. Each prefilled syringe contains a 1 mL glass syringe with a fixed 27 gauge ½ inch needle with needle guard.
Intended Users	Patients, caregivers, health care provider
Intended Use Environment	Home or medical setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On August 25, 2020, we searched the L:drive and AIMS using the terms, 'skyrizi' and 'risankizumab' to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified 8 previous reviews [8,9,10,11,12,13,14,15], and we considered our previous recommendations to see if they are applicable for this current review, and we confirmed that our previous recommendations were considered.

[8] Patel, M. Labeling Review for Skyrizi (BLA 761105/S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 16. RCM No.: 2019-2349.

[9] Schlick, J. Use-related Risk Analysis Review for Skyrizi (b) (4)) Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 01. RCM No.: 2019-1199.

[10] Schlick, J. Human Factors Results and Label and Labeling Review (BLA 761105/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 01. RCM No.: 2019-935 and 2019-1029.

[11] Patel, M. Label and Labeling Review Memo for Skyrizi BLA 761105. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 20. RCM No.: 2018-886-2.

[12] Patel, M. Label and Labeling Review Memo for Skyrizi BLA 761105. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 08. RCM No.: 2018-886-1.

[13] Patel, M. Human Factor Results and Label and Labeling Review for risankizumab BLA 761105. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 OCT 22. RCM No.: 2018-886 and 2018-910.

[14] Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 27. RCM No.: 2017-1719-1.

[15] Abraham, S. Human Factor Protocol Review for risankizumab IND 113306 (b) (4). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 22. RCM No.: 2017-1294 and 2017-1719.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:
\\CDSESUB1\evsprod\bla761105\0074\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hfeue-nsp150\human-factors-suppl-info.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\cdsesub1\evsprod\bla761105\0074\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hfeue-nsp150\human-factors-report-nsp150mgsupplement.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

We sent an information request to the Sponsor on August 31, 2020 requesting additional information on medication history of the participants, root cause analysis for all use errors observed, and clarification on the to-be marketed syringe sleeve portion of the user interface, as well a user group characteristics. The Sponsor provided a response on September 8, 2020 with their rationale.

The link to the information request response can be found at:

\\CDSESUB1\evsprod\bla761105\0082\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hfeue-nsp150\agency-response-2020-aug-31.pdf

We sent an information request to the Sponsor on October 2, 2020 requesting additional information on cardboard sleeve and additional mitigation strategies proposed. The Sponsor provided a response on October 23, 2020 with their rationale.

The link to the information request response can be found at:
\\CDSESUB1\evsprod\bla761105\0092\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hfeue-nsp150\us-agency-responses-cmc.pdf

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[16] along with postmarket medication error data, we reviewed the following Skyrizi labels and labeling submitted by AbbVie, Inc..

- Container labels received on June 26, 2020

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

- Sleeve labeling received on June 26, 2020
- Paperboard Insert labeling received on June 26, 2020
- Carton labeling received on June 26, 2020, available from \\CDSESUB1\evsprod\bla761105\0074\m1\us\114-labeling\draft\carton-and-container\draft-carton-skyrizi-150mg-1ml-pfs-20064212.pdf
- Professional Sample Container label received on June 26, 2020
- Professional Sample Carton Labeling received on June 26, 2020, available from \\CDSESUB1\evsprod\bla761105\0074\m1\us\114-labeling\draft\carton-and-container\draft-carton-skyrizi-150mg-1ml-pfs-sample-20064210.pdf
- Prescribing Information, Instructions for Use, and Medication Guide (Images not shown) received on October 15, 2020, available from \\CDSESUB1\evsprod\bla761105\0088\m1\us\114-labeling\draft\labeling\neg-lbl-6933.pdf

E.2 Label and Labeling Images

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

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

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

Date of This Review:	December 28, 2020
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761105/S-010
Product Type:	Combination Product (Drug-Device)
Drug Constituent Name and Strength	Skyrizi(risankizumab-rzaa) Injection, 150 mg/mL
Device Constituent:	autoinjector
Rx or OTC:	Rx
Applicant/Sponsor Name:	**AbbVie Inc.**
Submission Date:	July 27, 2020, October 20, 2020, October 26, 2020
OSE RCM #:	2020-1621
DMEPA Human Factors Evaluator:	Murewa Oguntimein, PhD, MHS,CPH,CHES
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting):	Jason Flint, MBA, PMP
DMEPA Associate Director for Labeling	Mishale Mistry, PharmD, MPH

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761105/S-010 for Skyrizi (risankizumab-rzaa) injection, 150 mg/mL. The Applicant is seeking licensure for the 150 mg/mL strength in a single dose pre-filled autoinjector (AI).

1.1 PRODUCT DESCRIPTION

Skyrizi (risankizumab-rzaa) was approved under BLA 761105 on April 23, 2019 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Skyrizi is currently available as a 75 mg/0.83 mL prefilled syringe (PFS) . The recommended dose is 150 mg (two75 mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. AbbVie proposes to supply a 150 mg/mL strength in a single dose pre-filled autoinjector pen..

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

- On July 10, 2018, AbbVie, Inc. (applicant) submitted their proposed HF Validation study protocol for their proposed 150 mg/mL strength single dose autoinjector pen to seek the Agency feedback on the study methodology prior to conducting the study.[1] On October 10, 2018, we provided our recommendations to the Applicant for the protocol and instructions for use (IFU).[2] The applicant addressed our deficiencies and implemented our recommendations prior to conducting their HF validation study.
- On July 27, 2020, the Applicant submitted their HF validation study results to support the proposed 150 mg/mL autoinjector[3], which is the subject of this review.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**

[1] Konkowski M. Human Factors Validation Study Protocol. (b) (4) . North Chicago, IL. 2018 JUL 10. \\CDSESUB1\evsprod (b) (4) 0161\m1\us\112-other-correspondence\request-comments-advice-ind\req-comments-advice-human-factors-protocol-ai.pdf

[2] Patanavanich S. Human Factors Validation Study Protocol Advice (b) (4) Silver Spring, MD. FDA, CDER, DMEPA.(US);2018 OCT,10. RCM:2018-1479 https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804bc405&_afrRedirect=2211312550272242

[3] Konkowski M. Human Factors Validation Study Report. BLA761105/S-010 . North Chicago, IL. 2020 JUL 27.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design (Table 2), errors/close calls/use difficulties observed (Table 3), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The study design is summarized in Table 2 below.

Table 2: Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	<table><tr><th rowspan="2">Group</th><th colspan="2">Trained</th><th colspan="2">Untrained</th><th rowspan="2">Total</th></tr><tr><th>Injection Naïve</th><th>Injection Experienced</th><th>Injection Naïve</th><th>Injection Experienced</th></tr><tr><td>Patients (PsO, PsA)</td><td>5</td><td>11</td><td>5</td><td>10</td><td>31</td></tr><tr><td>Caregivers</td><td>5</td><td>10</td><td>7</td><td>8</td><td>30</td></tr><tr><td>HCPs</td><td>0</td><td>0</td><td>1</td><td>14</td><td>15</td></tr><tr><td>Total</td><td>10</td><td>21</td><td>13</td><td>32</td><td>76</td></tr></table>
Training	Training was provided to the trained group of 16 patient and 16 caregiver participants. No training was provided to the untrained group of 15 patient, and 15 caregiver, and 15 HCP participants.
Test Environment	Simulated home setting

Sequence of Study	Trained Group: Training Session→24-26-hour decay period → simulated use scenario → Post-Use Interview to assess root causes for any use errors, close calls, or difficulties → Knowledge Task Questions (KTQs) → Post-Use Interview to assess root causes for any failures → hand measurement → Administered the Newest Vital Sign (NVS) to assess health literacy. Untrained Group: Simulated use scenario → Post-Use Interview to assess root causes for any use errors, close calls, or difficulties → KTQs → Post-Use Interview to assess root causes for any failures → hand measurement → Administered the NVS to assess health literacy.

3.2 RESULTS AND ANALYSES

Table 3 describes the study results, **AbbVie Inc.**'s analyses of the results, and DMEPA's analyses and recommendations.

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Select injection site (C)	**2 use errors** (b) (6) **Untrained)** The participant indicated they would inject into the outer thigh on the left leg. The moderator confirmed with the participant where they would inject, and the participant indicated they would inject between the hip and the		(b) (6) The participant indicated she always injects her uncle into the side of his thigh. She stated that she believed the medicine would "spread more evenly" and that there was "more fat" on the side of the thigh. She explained her prior injection experience had been with her diabetic uncle, and that she would typically clean and inject into the side of his thigh, saying	(b) (6) *Negative Transfer* had experience with an AI for diabetes medication, and typically injected that device into the side of the thigh. Rather than inject into the top of the thigh or abdomen, the participant used prior experience with injection devices to determine the	(b) (6) The instructions for this product were designed to recommend injections into the abdomen and thigh as those were identified as easier for self-injection but injection into the side of the thigh is medically acceptable. Injection into the side of the thigh is not associated with reduced safety or efficacy. Therefore, no mitigation strategies are needed.	We agree that negative transfer may have contributed to the root cause for this error (C12). Our review of the IFU determines that Step 3 of the IFU and Step 1 of the Quick Tips (QT) provide text, and both are accompanied by images of the injection site. Although the Applicant did not provide additional mitigation strategies, we find the IFU statements and images minimize the residual risk to the extent possible. Therefore, we have no further

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	knee. The moderator attached the injection pad and the participant delivered the injection into the side of the left thigh. The participant did not use the IFU or QTs during the injection task.		"that's what I always do for my uncle." The moderator asked the participant to point to where she would typically inject her uncle, and she pointed to the outside of the left thigh. She said that she learned to do this from other family members and from injecting her uncle.	injection site. Because of this, she injected into the side of the thigh, causing the use error.		recommendations at this time.

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	(b) (6) The participant perceived that the bottle of water provided with the supplies to be medication and the AI sharps container. The participant removed the cap from the AI thinking it was an oral syringe, pointed the	0	(b) (6) When asked how the participant knew to deliver the medication orally, he explained that it was because it was liquid (the bottle of water) and therefore it should be delivered orally. The participant was not aware that the AI contained the medication and a needle, stating that he "didn't think the medicine was in there yet." He	*Negative Transfer* (b) (6) thought that the AI was an oral syringe that needed to be filled prior to administering the medication. Because his only experience with syringe-like devices was oral administration, the participant made assumptions about the AI	(b) (6) Oral ingestion of the drug without injection taking place (e.g., attempting to squirt the drug into the mouth from the AI) is prevented by the AI needle shield and force requirements to displace the shield. No drug is delivered as an outcome. For the first outcome, the user would be unable to activate the device and likely report this using help line support or contacting the HCP. This would result in the user being instructed on the correct use of the device. Additional mitigations	We agree that negative transfer and test artifact may have contributed to the root cause for this error. We also note that the AI needle shield and force requirement to displace the shield would prevent the drug from being administered into a mouth structure (e.g., tongue) because to inject the AI, the user needs to push and keep pressing the AI down against the raised injection site, which may be difficult to do based on the structure of the mouth. Therefore, the

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	needle end into the sharp's container, and attempted to draw the water into the syringe using the green button on the device (the needle shield was not engaged so the AI did not activate). After the manikin was brought over to the participant, he indicated		further stated, "I saw here that this [AI inspection window] was empty so I thought that I was just trying to fill it … so I thought I would pick it up and I would use it to pull the substance." When probed why he did not look at the instructions prior to completing the task, the participant stated that he normally would look at instructions and that he thinks he	prior to attempting the task. The participant did not look at the IFU or the QT prior to completing the task.	include IFU and web-based training videos that the user may engage after failing to inject. No further mitigation is needed. Another outcome, injection into a mouth structure (e.g., tongue), is associated with pain potentially requiring medical attention. It is unlikely an entire dose can be delivered due to pain and so this is associated with the patient receiving less drug than intended. For the second outcome, the design of the AI requires an even injection surface	design of the AI has been optimized to prevent this use error. In addition, we determined that Step 3 of the IFU and Step 1 of the Quick Tips (QT) provide text, and both are accompanied by images of the injection site. The carton labeling also clearly state the correct route of administration (i.e.subcutaneous). Although the Applicant did not provide any additional mitigation strategies, we find the AI design, IFU statements and images minimize the residual risk to the extent

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	that he would administer the medication by putting a "few drops in the mouth." The moderator intervened when the participant attempted to activate the AI into the mouth of the manikin. The participant did not use the IFU or QT to complete the task.		was overeager to explore the new device.		and force threshold to engage the shield for activation that is not available or feasible on a mouth structure. The design acts as a failsafe to injection into non-subcutaneous areas. This risk is therefore sufficiently minimized, and no further mitigation is needed.	possible. Therefore, we have no further recommendations at this time.

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
Remove the AI cap (C)	**1 use error** (b) (6) The participant chose the correct injection site on their abdomen, correctly oriented the device, and then positioned the AI over the site without removing the cap. He pressed down against the	0	(b) (6) stated that he did not remove the cap, "I didn't take it off intentionally,"from the device because he "didn't want to waste the product," stating "It's a simulation." The participant felt that since the injection process was "the same concept" as his previous AI, there was no need to waste medication.	(b) (6) *Test Artifact of Simulated Use* The participant went through the correct motions to administer the medication, but intentionally left the cap on the device so as not to waste the product in the simulated testing environment.	This is an artifact of simulated use and not a circumstance that would be seen in clinical practice. Therefore, no mitigation strategies are needed.	We agree the root cause of this error was a misunderstanding of the scenario (i.e., test artifact). We also determined that (b) (4) (b) (4) of the IFU, and of the QT provide text, and both are accompanied by images of removing the AI cap. Additionally, the AI design includes a dark gray cap with a white arrow pointing down, which gives a visual cue to the user to remove the cap. The AI design, IFU and QT statements and images minimize residual risk to the extent possible.

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	injection site, pushed the button, then removed the AI and disposed of it in the trash, believing that he had correctly administered the full dose of medication. The participant had the IFU partially opened on the table during the simulated injection but					Therefore, we have no recommendations at this time.

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	did not utilize the instructions.					
Hold down for the entire injection (c)	**2 use errors (C12- Caregiver Untrained)** The participant pressed the AI against the injection pad without pinching the skin and quickly pressed the green button. She held the pen against the pad for 8 seconds, then	0	**(C12)** the participant stated that she had intended to hold the device against the pad for three seconds. When asked why she would hold for three seconds, she said that after counting slowly to three, all the medicine should have been delivered into the pad. The participant indicated she knew this based	**(C12)** *Negative Transfer* The participant had previous experience with an AI for diabetes medication and would typically count to three when delivering an injection with that device. The participant assumed the test device would function	**(C12)-**Wet injections were identified as a use error during hazard analyses completed for this product and multiple design elements are included to mitigate the error (e.g., the yellow indicator in the inspection window, the second click audible indicator, IFU, QT, online support and videos). These design elements were subjected to multiple iterative design cycles that included simulated use testing with representative users to minimize the risk to the extent	We note the potential harm associated with these errors is an underdose which may result in the patient receiving inadequate treatment. We acknowledge the Applicant's labeling mitigations. Based on our review, we've identified additional labeling mitigations to address this error (by participant C23). Our heuristic review of the QT determined that in step 4 " push and hold", the phrase "15 seconds" is not

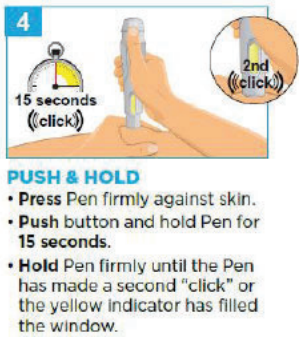
Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	lifted the pen while the medicine was still being delivered, causing some liquid to spray onto the injection pad. The participant attempted to recap the device, but the moderator took the device from her. The participant indicated she had completed		on prior experience with injecting her uncle and from watching her mother and grandmother inject as well, saying "when you inject it for three seconds and count slowly, all the medication is supposed to go inside." When asked about the device she had used in the past, she indicated the instructions for it did not specify to hold for three seconds, but	similarly, causing her to count to three during the injection task. Because of this, she lifted the device prematurely, causing the full dose not to be delivered.	possible. No additional mitigations are available to reduce this risk further.	prominent and the word "1st" is missing next to the word "click" as there is the word "2nd" next to the second "click".  Therefore, we recommend adding the word "1st" next to the word "click". In this instance, we have determined that

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	the task. The participant did not view the IFU or QT during the task.		that she had been taught that approach by her uncle and family.			the proposed changes to the QT do not require submission of additional human factors data.
	-(C23-Caregiver Untrained) (C23) The participant cleaned the injection site with an alcohol swab, squeezed the skin, and pressed the injector into the injection pad. She pressed the	0	**(C23)** During the injection task, the participant returned to the QT and said that she "didn't see the 15 seconds" when she noticed that the medication dripped onto the injection pad. During the follow-up questions, the participant reiterated, "I read the directions,	**(C23)** *Insufficient Prominence of Guidance* The participant removed the injector after the first click, believing the injection had been completed immediately. The participant indicated that	**(C23)** Wet injections were identified as a use error during hazard analyses completed for this product and multiple design elements are included to mitigate the error (e.g., the yellow indicator in the inspection window, the second click audible indicator, IFU, QT, online support and videos). These design elements were subjected to multiple iterative design cycles	

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	green activator button, then removed the device approximately one second later, before the second click. Upon removing the injector, the participant noticed that there was liquid coming out of the device and onto the injection pad. The participant used QT and		but I didn't fully read it where it says you have to let it stay in for 15 seconds." The participant also stated that she did not notice the "15 seconds" in the picture even after she re-read the instructions.	she did not read the instructions on the QT fully during the task and reiterated it again during follow-up questions. The participant also did not look at the images on the QT during or after the task, until probed by the moderator about the images during follow-up.	that included simulated use testing with representative users to minimize the risk to the extent possible. In addition, this participant did notice the wet injection and then returned to the QT where she identified the need to hold for 15 seconds. A user encountering a similar scenario where the error has been recognized may report this using help line support or contact the HCP. This would result in the user being instructed on the correct use of the device. No additional mitigations are available to reduce this risk further.	

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	did not refer to the IFU.					
Table 2: Summary and Analyses of Study Results- Knowledge Assessments associated with high severity /low probability outcomes						
According to the instructions, what should you do if the AI has been damaged? (E)	**2 failures Trained Patient** (b) (6) The participant was unable to locate information in the IFU directing them not to use the AI if it has been dropped or damaged. The participant said they	0	(b) (6) "I know you need to trash it, but I don't see that. I don't see the word damaged." The participant was unable to locate information in the IFU directing them not to use the AI if it has been dropped or damaged. The participant said they should dispose of the device but was unable to locate	(b) (6) *Insufficient Prominence of Guidance* The participant indicated they were looking for the word "damaged" in the IFU but didn't see it. When the participant noticed the relevant direction in the IFU, they indicated they were originally	(b) (6) AI design and manufacturing processes reduce the risk that a user will receive a damaged pen. As in this instance, where the user recognized damage has occurred and does not use the AI, in contacting the HCP or product support, the user would receive a replacement AI. No additional mitigations are needed to reduce this risk further.	The potential harms associated with not finding this information and using a damaged device include 1) an incomplete injection due to AI damage and suboptimal treatment of the condition that may require medical attention, and 2) physical trauma during use of the damaged device (e.g., laceration, puncture, abrasion). However, our review of the IFU determines that the important information

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	should dispose of the device but was unable to locate the relevant section in the IFU. "I know you need to trash it, but I don't see that. I don't see the word damaged."		the relevant section in the IFU.	looking for it in the Important Information section but didn't see directions telling them not to use the device. The participant was unable to locate the correct answer due to insufficient prominence of text, and the participant's attempt to locate matching text.		section does include a statement that the AI should not be used if dropped or damaged, and the words "dropped and damaged" are bolded for prominence. Therefore, although the Applicant did not provide any additional mitigation strategies, we find the IFU statement minimizes the residual risk to the extent possible. Therefore, we have no further recommendations at this time.
	Untrained	0	(b) (6) "Thawed, this	(b) (6) *Insufficiently*	(b) (6) AI design and manufacturing processes	

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	Caregiver (b) (6) The participant was unable to locate information in the IFU directing them not to use the AI if it has been dropped or damaged. The participant understood they should not use the device but		means once? Is this the past tense of thrown away? Step 1, do not use it, does expired count as damaged? Does not say but do not use it." The participant was unable to locate information in the IFU directing them not to use the AI if it has been dropped or damaged. The participant understood they should not use the device but was unable to locate	*Prominent Guidance* While the participant was unable to locate the correct information when asked the question, later in the Knowledge Assessment they noticed information in the "Questions" section directing them not to use the device. During follow	reduce the risk that a user will receive a damaged pen. As in this instance, where the user recognized damage has occurred and does not use the AI, in contacting the HCP or product support, the user would receive a replacement AI. No additional mitigations are needed to reduce this risk further.	

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	was unable to locate the relevant section of the IFU. "Thawed, this means once? Is this the past tense of thrown away? Step 1, do not use it, does expired count as damaged? Does not say but do not use it."		the relevant section of the IFU.	up questioning, the participant indicated they were only looking at the steps on the front of the IFU and did not flip it over to view the back. The moderator also noted the participant struggled with language in the IFU and asked the moderator for clarification and		

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
				definitions of some words throughout the knowledge assessment		
According to the carton, what should you do if you received this carton and it was already opened? (E)	**1 failure Untrained Caregiver** (b) (6) The participant was unable to locate information on the carton directing them to return the carton to the pharmacist if it has been opened. The	0	(b) (6) "If it is already opened, I would not use it… It does say on the box to 'Disregard' different things after use, do not reuse, store the pens in the carton until time of admission. I wouldn't want anything to be damaged so I wouldn't use it unless it were	(b) (6)) *Insufficiently Prominent Guidance* The participant stated that during the task, they first noticed the 'Lift here to open' and looked there for what to do about tamper evidence.	(b) (6) Standard packaging controls mitigate harm associated with this failure (i.e., use of product with compromised package integrity). A modification was also recommended to the carton label text to improve prominence and noticeability. This modification recommendation was implemented. The modification moves the "Return to pharmacy if	We note the potential harm associated with using the product when the perforation seal is broken may result in counterfeit toxic material administered to the patient. Our review of the mitigation strategy that was implemented by the Applicant to move the "Return to pharmacy if carton perforations are broken." label text above the "ATTENTION

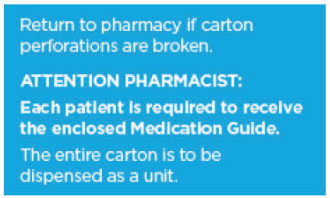
Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
	participant understood they should not use the device but was unable to locate the relevant instruction on the carton.		sealed because of the warning signs on the label. It only says the carton is to be dispensed as a unit, and I don't see if it says anything different." The participant was unable to locate information on the carton directing them to return the carton to the pharmacist if it has been opened. The participant understood they should not use the device but was	When the moderator pointed out the tamper evidence instruction, the participant stated that "because it says 'Attention Pharmacist', it made me look elsewhere. I see now it says return to pharmacy." She said that she had not seen the tamper evidence instruction	carton perforations are broken." label text above the "ATTENTION PHARMACIST". BEFORE (b) (4) [redacted] AFTER  The residual risk is expected to be low due to the packaging controls identified above. The instruction modification is intended to improve	PHARMACIST" finds the carton labeling statement minimizes residual risk to the extent possible. Therefore, we have no further recommendations at this time. In this instance, we have determined that the sponsor's changes to the carton labeling do not require submission of additional human factors data.

Table 3: Summary and Analyses of Study Results- Simulated Use Tasks						
Tasks Evaluated (C for Critical and E for Essential)	**Number and Description of Use Errors**	**Number and Description of Close Calls and Use Difficulties**	**Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties**	**Applicant's Root Cause Analysis**	**Applicant's Discussion of Mitigation Strategies**	**DMEPA's Analysis and Recommendations**
			unable to locate the relevant instruction on the carton.	during the task because after seeing 'Attention Pharmacist', she assumed the entire section was for pharmacists and not applicable to her.	noticeability but is not expected to reduce the residual risk further. As a result, validation of the recommended instruction is not required.	

3.3 LABELS AND LABELING

Table 4 below includesthe identified medication error issues with the submitted, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. Our review of the prescribing information (PI) for the proposed product is under supplement review 009.[4]

[4] Patel, M. Human Factors Results and Labeling Review for BLA 761105/S009. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2020 DEC XX. RCM:2020-1366

Table 4: Identified Issues and Recommendations for AbbVie Inc. Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.Error! Reference source not found.(entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Quick Tips			
1.	In step (b) (4) (b) (4) (b) (4) (b) (6) Participant pressed the green activator button, then removed the device approximately one second later, before the second click.	The omission of this word may lead to confusion and under dose	Add the word (b) (4)
Instructions for Use (IFU)			
1.	Inconsistent terminology with use of "pinch" (QT) and (b) (4) (b) (4) (IFU)	Use of inconsistent terminology may lead to confusion.	Use "pinch" to minimize the risk for confusion.

Carton Labeling			
1.	The net quantity statement does not appear on the principal display panel.	The net quantity statement should appear on the principal display panel (PDP), but should be separated from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded).[5]	Revise the statement appearing at the top of the Principal Display Panel (PDP) from "Prefilled Single-Dose Pen" to read "One 1 mL Single-Dose Prefilled Pen" to include the net quantity statement, as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013
2.	It is unclear if there is enough white space surrounding the linear barcode on the carton labeling.	Lack of sufficient white space surrounding the linear barcode could make it difficult for scanners to reach the barcode correctly.	Please confirm there is sufficient white space surrounding the linear barcode. The barcode should be surrounded by sufficient white space to allow scanners to correctly read the barcode in accordance with 21 CFR 201.25(c)(i).

[5] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (lines 461-463). Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

4. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated use errors with some critical tasks that may result in harm. Furthermore,our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 4 for **AbbVie Inc.** We ask that the Division convey Table 4 in its entirety to **AbbVie Inc.** so that recommendations are implemented prior to approval of this BLA 761105- S10. In this particular instance, we have determined that the changes can be implemented without submission of additional HF validation testing data for the Agency's review.

4.1 RECOMMENDATIONS FOR ABBVIE INC.

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations prior to approval of this BLA 761105- S10. In this particular instance, we have determined that the changes can be implemented without submission of additional human factors validation testing data for the Agency's review.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 6 presents relevant product information for Skyrizi (risankizumab) that **AbbVie Inc.** submitted on August 8, 2020

Table 6. Relevant Product Information	
Initial Approval Date	Initial: April 23, 2019 for S-010: N/A
Therapeutic Drug Class or New Drug Class	interleukin-23 antagonist, is a humanized immunoglobulin G1 (IgG1) monoclonal antibody.
Active Ingredient (Drug or Biologic)	risankizumab-rzaa
Indication	treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.
Route of Administration	subcutaneous
Dosage Form	injection
Strength	Currently Approved: 75 mg/0.83 mL (90 mg/mL) Proposed: 150 mg/mL
Dose and Frequency	Currently approved: 150 mg (two 75 mg injections) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter. Proposed: 150 mg (one 150 mg injection) administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter.
How Supplied	Currently approved: Carton of two 75 mg/0.83 mL (90 mg/mL) in a single-dose prefilled syringe Proposed: Carton of one 150 mg/mL in a single dose pre-filled pen.
Storage	Store in a refrigerator at 2° C to 8° C (36° F to 46° F)
Container Closure/Device Constituent	Currently approved: Carton containing 2 prefilled syringes and 2 alcohol pads. Each prefilled syringe contains a 1 mL glass syringe with a fixed 29-gauge ½ inch needle with needle guard. Proposed: Carton containing 1 single dose prefilled autoinjector pen, 1 IFU and one PI with medication guide. The single dose autoinjector pen consists of a green activator button, gray hand grips, inspection window, white needle sleeve, needle and a dark gray cap.

	(b) (4)
Intended Users	Patients, caregivers, health care provider
Intended Use Environment	Home or medical setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On November 10, 2020 we searched the L:drive and AIMS using the terms, BLA 761105, Skyrizi and Risankizumab to identify reviews previously performed by DMEPA.

B.1.2 Results

Our search identified 4 previous reviews[6][7][8][9][10][11][12][14][15][16][17] and one interaction[18] and we confirmed that our previous recommendations were implemented or considered.

[6] Abraham, S. Human Factors Validation Study Protocol Review for (b) (4) IND 113306. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2017 NOV 27. RCM:2017-1719

[7] Mena-Grillasca, C. Proprietary Name Review for BLA 761105. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2018 JUL 6. RCM:2018-22597352

[8] Patel, M. Human Factors Validation Study Protocol Review for (b) (4) Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2018 SEP 14. RCM:2018-1479

[9] Patel, M. Human Factors Results and Labeling Review for BLA 761105. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2018 OCT 22. RCM:2018-886-1

[10] Mena-Grillasca, C. Nonproprietary Name Suffix Review for BLA 761105. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2019 FEB 7. RCM:2018-883

[11] Patel, M. Review of Revised Label and Labeling for BLA 761105. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2019 MAR 20. RCM:2018-886-2

[12] Schlick, J. Human Factors Results and Labeling Review for BLA 761105-S-001. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2019 AUG 1. RCM:2019-935

(b) (6)

[14] Barlow, M. Human Factors Protocol Review for IND 118701 and IND133100. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2019 NOV 07. RCM:2019-1881

[15] Patel, M. Labeling Review for BLA 761105-S-005. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2019 DEC 16. RCM:2019-2349

[16] Barlow, M. Response to Human Factors Protocol Clarification Question for IND 118701 and IND133100. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2020 APR 21. RCM:2019-1881-1

[17] Barlow, M. Response to Human Factors Protocol Clarification Question for IND 118701 and IND133100. Silver Spring (MD): FDA,CDER, OSE, DMEPA (US); 2020 OCT 2. RCM:2019-1881-2

[18] Antinello, C. IND 113306 Type C Meeting-Final Written Response Letter. Submitted to DARRTS on JULY 18, 2019. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80531685&_afrRedirect=944834341736392

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:

(b) (4)

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\bla761105\0079\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hfeai\human-factors-report-ai.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On October 16, 2020, the Agency sent an Information Request to the Applicant which requested the Applicant provide the average injection time and details on the relationship between the time when the second click is heard and when the window turns yellow to aide in the review of their HF validation study result. The Sponsor provided an acceptable response on October 20, 2020. See link: \\CDSESUB1\evsprod\bla761105\0091\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hfeai\us-agency-responses-cmc.pdf

On October 23, 2020, the Agency sent an Information Request to the Applicant which requested the Applicant provide the root cause analysis, participants' subjective feedback, and discussion of residual risks for study participants who did not hold down the autoinjector for 15 seconds as specified in the IFU, to aide in the review of their HF validation study result. The Sponsor provided an acceptable response on October 26, 2020. See link: \\CDSESUB1\evsprod\bla761105\0093\m5\53-clin-stud-rep\535-rep-effic-safety-stud\psoriasis\5354-other-stud-rep\hfeai\us-agency-response-cmc.pdf

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

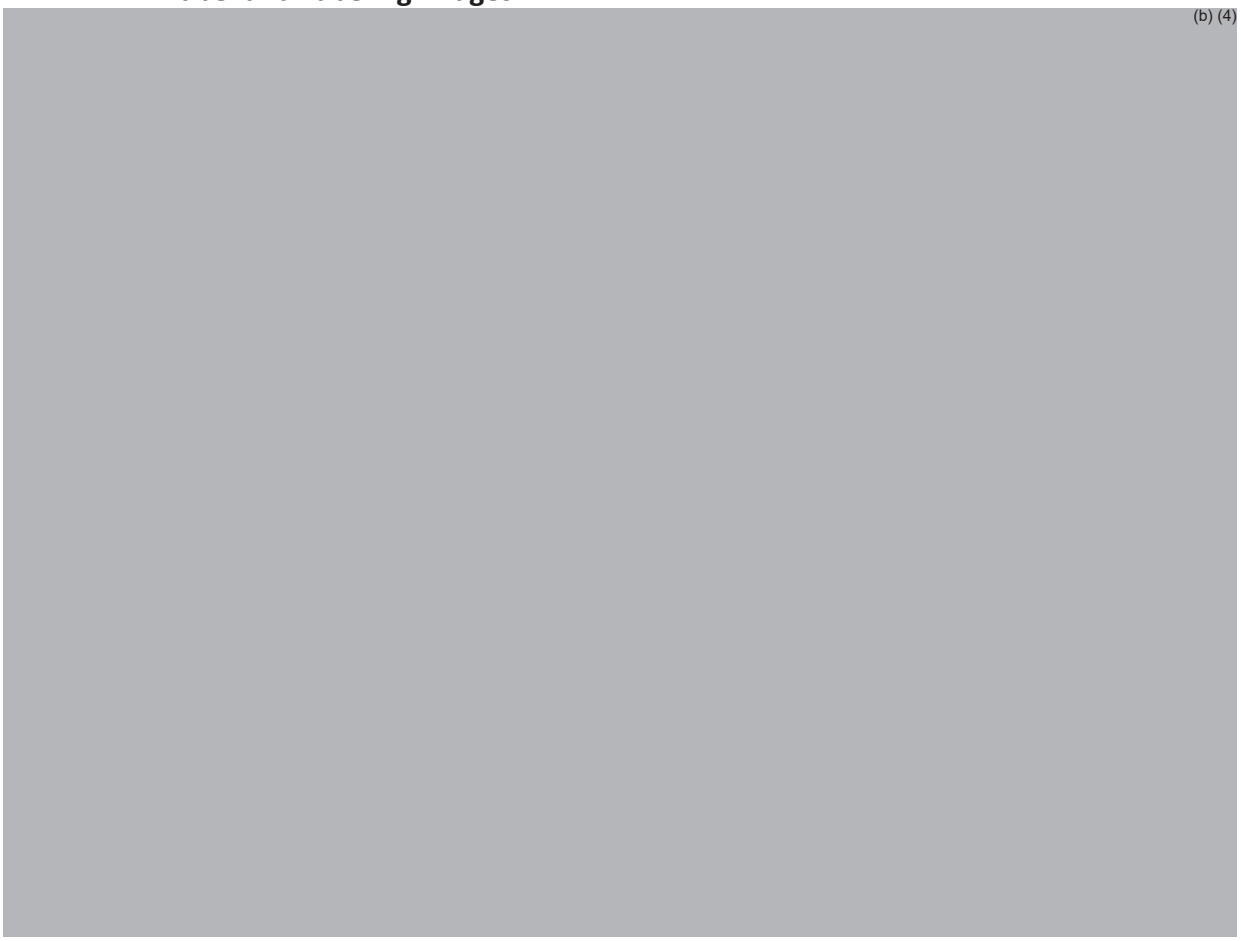
Using the principles of human factors and Failure Mode and Effects Analysis,[19] along with postmarket medication error data, we reviewed the following Skyrizi (risankizumab) labels and labeling submitted by **AbbVie Inc.**

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

- Container label received on August 8, 2020
- Carton labeling received on August 8, 2020
- Instructions for Use received on August 8, 2020
- Medication Guide (Image not shown) received on August 8, 2020 \\CDSESUB1\evsprod\bla761105\0079\m1\us\114-labeling\draft\labeling\local-lbl-4351.docx
- Prescribing Information (Image not shown) received on August 8, 2020 \\CDSESUB1\evsprod\bla761105\0079\m1\us\114-labeling\draft\labeling\local-lbl-4351.docx

E.2 Label and Labeling Images

(b) (4)



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/s/

OLUWAMUREWA OGUNTIMEIN
12/28/2020 06:19:06 PM

MILLIE B SHAH
12/29/2020 03:34:35 PM

JASON A FLINT
12/29/2020 03:39:45 PM

MISHALE P MISTRY
12/29/2020 03:41:27 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s009/010

OTHER REVIEW (s)

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	3/15/2021		
To:	ANH-THY LY		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	N/A-OPQ/OSE led
From	Rob Nakielny OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Director OPEQ/OHT3/DHT3C		
Subject	BLA 761105 , SKYRIZI (risankizumab-rzaa) ICC2000658, 2000659, 2000676 Case #00025444, 00025445, 00025806		
Recommendation	**Filing Recommendation Date: 8/25/2020** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. see Section 5.4 Filing Review Conclusions ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☑ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: Click or tap to enter a date. ☐ Device Constituent Parts of the Combination Product are Approvable. ☑ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761105 (Supplement Sequence 0074 and 0079
Sponsor	AbbVie Inc.
Drug/Biologic	SKYRIZI (risankizumab-rzaa)
Indications for Use	Treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Device Constituent	Pre-Filled Syringe, Autoinjector
Related Files	None

Review Team		
Lead Device Reviewer	*Rob Nakielny*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A	N/A	N/A

Important Dates	
Interim Due Dates	**Meeting/Due Date**
Filing	08/25/20, 09/25/20
74-Day Letter	
Mid-Cycle	
Primary Review	2/26/21
Internal Meeting(s)	
Sponsor Meeting(s)	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☑ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	x			N/A
Labeling	x			N/A
Design Controls	x			Adequate with IR#1 received 2/18/21
Risk Analysis	x			Adequate with IR#1 received 2/18/21
Design Verification	x			Adequate with IR#1 received 2/18/21 and with proposed PMC (see section 2.3 below)
Consultant Discipline Reviews			x	N/A
Clinical Validation			x	N/A
Human Factors Validation			x	N/A
Facilities & Quality Systems	x			Adequate with IR#2 received 3/8/21 and with proposed PMC (see section 2.3 below)

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☑
CDRH does not have Post-Market Commitments or Requirements	☐

Post-Market Commitment or Requirement:

Recommendation for Post Market Commitment (6 months to a year timeframe) to either place added Design Input Requirements around the volume level and the timing of the audible cue or to control the design criteria which these characteristics are dependent on (Critical Design Features)

To the sponsor:

For your AutoInjector, you state that the user needs to be able to determine if the dose was administered successfully, and therefore designed your combination product to indicate by auditory means to the user, that the injection process is complete. However, there is no specific acceptance criteria or related after-assembly release testing for this audible feedback (click sound volume, timing, correlation with dose delivery) function of your device to ensure that the quality of this attribute as designed is effectively and reliability maintained. Your intended user may solely rely on the audible feedback to indicate end of injection, therefore either,

.

1) Implement and validate component inspection criteria specific to those design dimensions which are critical to maintain that the "hammers" of the control unit disengage at the stated fixed nomial distance relative to the end of the syringe barrel in order to achieve no more than 0.05mL at the time of the audible click. In addition, implement and validate component inspection criteria for those design dimensions which are responsible for the audible click volume.

Or

2) Implement and provide verification testing of design input requirements and assembly release testing for your audible click volume (i.e., decibels) and timing (+/- seconds from end of injection) or residual volume after click (delivered volume remaining in device after audible click.

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1.Scope

AbbVie Inc. is requesting approval of SKYRIZI (risankizumab-rzaa). The device constituent of the combination product is a Pre-Filled Syringe with Needle Stick Prevention (PFS-NSP) per supplement #9 and an Auto-Injector (AI) per supplement #10 .

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Review of the submitted AI/NSP-PFS to support approval of the new routes of administration.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Both NSP-PFS, AI: Device performance, Biocompatibility (non-drug contacting, AI and PFS), Essential Performance Requirments (EPR) Control Strategy, Stability (device performance on stability) AI only: QS review /Inspection status

This review will not cover the following review areas:

- Compatibility of the drug with the device materials
- Biocompatibility of the primary container closure, including needle
- Sterility (primary container closure sterility)
- Human Factors

The sponsor clarifies that primary container/PFS components are the only which have fluid contact or are fluid path contacting; therefore, this means that CDER CMC reviewers will address the potential for leachables/extractables of these materials into the drug product, which adequately addresses biocompatibility from CDRH assuming that this data is found to be adequate. Given this information, CDRH will only address biocompatibility of the SS and AI surface/skin contacting components.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product; however, the original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2.Prior Interactions

Per section 1.6.3 Correspondence Regarding Meetings, 150 PFS – Correspondence – Meetings, the following questions related to the presentations of the Conbination Product were addressed in June of 2015 with the FDA (IND 113306)

Question 22:
Does the Agency concur that registration of the combination product, BI 655066- Autoinjector (AI); will be fully supported upon completion of the following studies in addition to the technical evaluations:

- formative and summative human factors studies with autoinjector
- pharmacokinetic bridging study (autoinjector vs. pre-filled syringe)
- real life patient handling study (RLHS) in patients with psoriasis using the to be-marketed autoinjector

Response:
Yes, we agree as long as the PK bridging study will be conducted between 150 mg/mL auto-injector vs. 150 mg/ml pre-filled syringe.

In addition, we request that you submit the following:

1. A detailed summative Human Factors protocol for review and feedback prior to starting the study.
2. A summary and analysis of your formative studies results.
3. Discussion of changes made to your product after the formative studies, including how the results from the formative studies were used to update the user interface and use-risk analysis.

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4. An updated use-risk analysis.
5. Instructions for Use and Quick Reference Guide in MS Word format.

Send three samples of the proposed Auto Injector with your submission.

Within the briefing package you state that you will reference "FDA Guidance for Industry, Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products", as well as specific international consensus standards that are included within this guidance for the development of your auto-injector. This approach appears to be acceptable; however the Agency wishes to remind you that, as part of the future investigational and marketing submissions, we expect that you will implement device constituent part requirements and specifications, associated acceptance criteria, and verification/validation activities in the context of the injector's intended use (patient population, environment of use, and medication to be delivered).

Question 23:
Does the Agency concur that beyond the Human Factors Studies (HFS) and analytical comparability as discussed in Question 19, no clinical studies, such as pharmacokinetic (PK) bridging are required to support registration and use of the PFS equipped with a needle safety device (NSD)?

Response:
Yes, we agree.

Question 24:
Does the Agency concur that there is no need to conduct Human Factor Studies (HFS) for the pre-filled syringe (PFS) without needle safety device (NSD)?

Response:
Yes, we agree.

3.2.1. Related Files

3.3.Indications for Use

Combination Product	Indications for Use

SKYRIZI (risankizumab-rzaa)	Treatment of moderate-to-severe plaque psoriasis in adults who are candidates fo rsystemic therapy or phototherapy
Pre-Filled Syringe & Auto-Injector	Delivery of the Drug Product

3.4.Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0074 (supplement 9)	3.2.Body of Data
0079 (Supplement 10)	3.2 Body of Data
0001	3.2.R Regional Information
0101	3.2 R Regional Information, 1.11 Quality Information Amendment
0106 / 0107 response to IR #2 (control plan)	
0113 / 0114 response to IR #3 (reliability, audible cue)	

4. DEVICE DESCRIPTION

4.1.Device Descriptions

The "container closure/PFS for 150 mg/ml SKYRIZI (risankizumab-rzaa) is assembled with additional components into a safety syringe (SS-PFS) or autoinjector (AI), which are the final device presentations. The prefilled syringe is the same for both designs. See the device description for each device constituent below:

Sequence 74 PFS+NSP

The Pre-filled Syringe + Needle Stick Prevention is for subcutaneous administration of Risankizumab 150 mg/mL.

PFS

The Sterile Pre-filled Syringe (PFS) consists of a 1 mL glass syringe, utilizing USP/Ph. Eur./JP Type I borosilicate glass.

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Table 1. Description and Specifications for Components and Sub-assemblies (continued)

4.2.Steps for Using the Device

NSP+PFS:

1. Inspect drug product through viewing window
2. Remove needle cover
3. Insert needle for subcutaneous injection (at about a 45-degree angle)
4. Depress plunger
5. Pull needle out of skin
6. At end of stroke, activate needle stick prevention mechanism by releasing pressure on plunger which withdraws needle into guard.

AI:

7. Remove RNS (Rigid needle shield) remover cover from the AI (which also removes needle cover from PFS).
8. Press against skin
9. Press the trigger button of the AI for delivery of the drug product solution. Hold for 15 seconds.
10. End of delivery, inspection window is yellow and audible click is presented.
11. Remove from skin

4.3.Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Device description of each device, PFS-NSP and AI, is adequate.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1.Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility (note: Device components are not required to be sterile – Only container closure which the review of sterility is deferred to CDER.)			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors			X

	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation			X
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment
The sponsor provided sufficient information to begin review.

5.2.Facilities Information

Firm Name:	Abbvie Deutschland Gmbh & Co. KG
Address:	Knollstrasse 67061 Ludwigshafen Germany
FEI:	3002807401
Responsibilities:	Final Assembly of the Auto-Injector drug product

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 6/19/2017 to 6/23/2017. The inspection covered both drug CGMPs and medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A post-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, a recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

Add Additional Facility

Reviewer Comment
Scope of the review of the assembly facilities is limited to the AI device only.

The proposed Post Approval Inspection is based on the fact that the last inspection of the manufacturing facility was performed 3 years ago; however, the manufacturing facility inspection at that time resulted in NAI, the facility is experienced in manufacturing medical devices, and the device is a non emergency use product.

5.3.Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☑ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A **Site(s) needing inspection: Abbvie Deutschland Gmbh & Co. KG**
Reviewer Comments **We are recommending Post-Approval Inspection for the AI manufacturing facility.**
Refuse to File Deficiencies: ☐ Yes ☐ No ☑ N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No ☑ N/A

6. LABELING

6.1.General Labeling Review

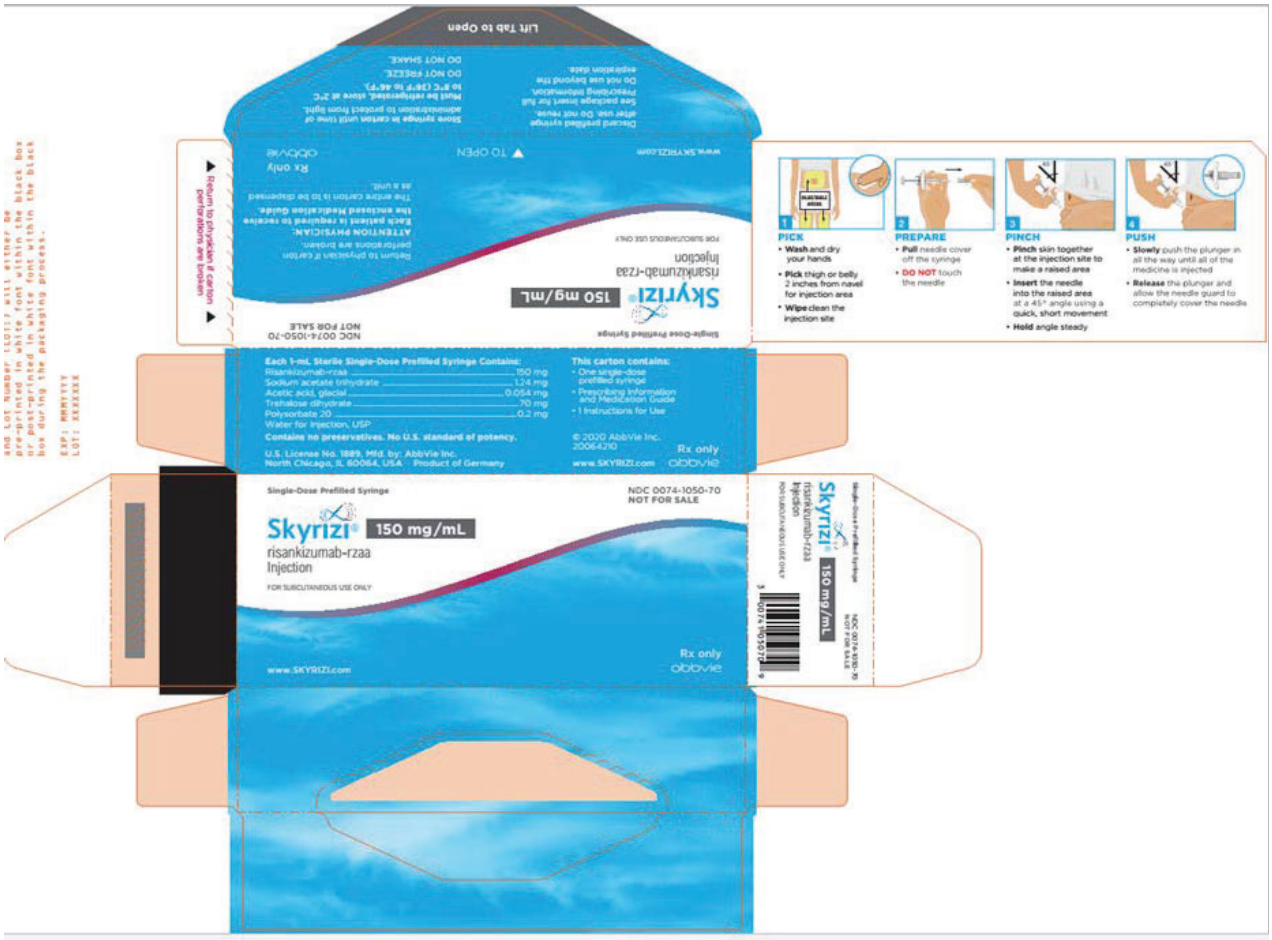
The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?			
	Yes	No	N/A	Comments
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X			N/A
Drug name is visible on device constituent and packaging	X			See seq 0074/79, 1.14.1.1,
Device/Combination Product Name and labeling is consistent with the type of device constituent	X			N/A
Prescriptive Statement/Symbol on device constituent	X			N/A
Warnings	X			N/A
Contraindications	X			N/A
Instructions for Use	X			N/A
Final Instructions for Use Validated through Human Factors	X			Human Factors validation testing is provided 0074/0079– 5.3.5.4 Note – The review of this information is deferred to CDER/OSE/DMEPA

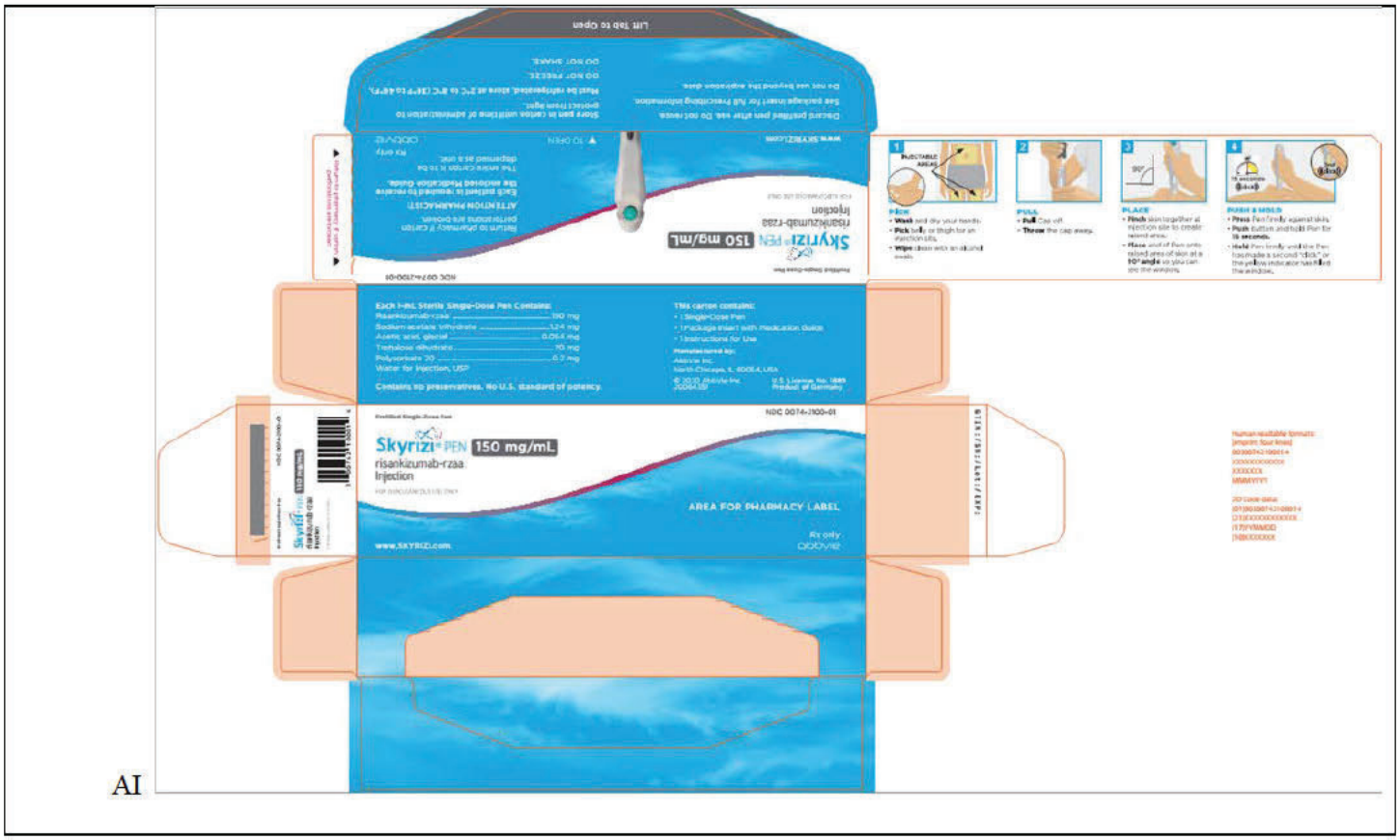
Reviewer Comments
In section 1.14 of each sequence 74 and 79, the sponsor provided the labeling information for each presentation of the combination product.

- The Sponsor provided the final packaging cartons for each product. Below is an image of each, the NSP+PFS carton labeling and the AI +PFS carton labeling.
- The sponsor provided the instructions for use for both the NSP+PFS and AI+PFS

CDER/OSE/DMEPA will review human factors validation to support that the instructions for use are adequately validated.



NSP+PFS



Reviewer Comments

The instructions for use and carton/product labeling for the prefilled syringe and autoinjector were complete. CDER/OSE/DMEPA will review human factors validation to support that the instructions for use is adequately validated.

6.2.Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments **The Labeling and Instructions for Use is Adequate.**		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1.Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	Comments
Risk analysis conducted on the combination product	X		N/A
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		NSP-PFS – (Hazard Analysis located in Seq0001 3.2.R Regional Information, risk Management Information) NFP-PFS and AI System Risk Asssessment (SRA table) in 3.2R Regional Information
Mitigations are adequate to reduce risk to health	X		NSP-PFS – Yes AI – Yes
Version history demonstrates risk management throughout design / development activities	X		Yes
Design Inputs/Outputs	**Yes**	**No**	**Comments**
Design requirements / specifications document present (essential performance requirements included)	X		Product requirements listed in seq 0074/0079, 3.2.P.2 Pharmaceutical Development, section 5.2 Product Requirements. EPR's in seq0001/0079 3.2.R Regional Information, Essential Performance
Design Verification / Validation Attributes	**Yes**	**No**	**Comments**
Validation of essential requirements covered by clinical and human factors testing	X		Human factors summative testing only for NSP-PFS. Clinical and Human Factors testing for AI
To-be-marketed device was used in the pivotal clinical trial		X	AI – yes NSP-PFS – no; however justification provided in 3.2.P.2 Bridging Clinical to Commercial Drug Product justification (supplemental human factors study with to be marketed device).
Bioequivalence Study utilized to-be-marketed device	X		Phase 1 study in healthy subjects submitted in the June 26, 2020 sBLA that demonstrate the bioequivalence between the risankizumab 150 mg/mL PFS and the marketed 90 mg/mL PFS, as well between the 150 mg/mL AI and the 150 mg/mL PFS
Verification methods relevant to specific use conditions as described in design documents and labeling	X		Yes

Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		Sponsor relies on ISO 11608 and other recognized standards for testing. There are no additional testing reliability requirements or recommendation from the Agency based on risk.
Traceability demonstrated for specifications to performance data	X		seq0001/0079, 3.2.R Regional Information, Trace Matrix

Reviewer Comments

It should be noted that it is DHT3C's internal policy is to not review Prefilled Syringe functionalities outside of the needle safety device (NSD) performance; i.e. NSD activation, lockout, etc. The PFS-SS performance such as dose accuracy and breakloose and glide force will not be addressed within this review.

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Summary of Design Contol appears complete

7.2.Design Inputs and Outputs

Essential Performance Requirements

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[redacted]

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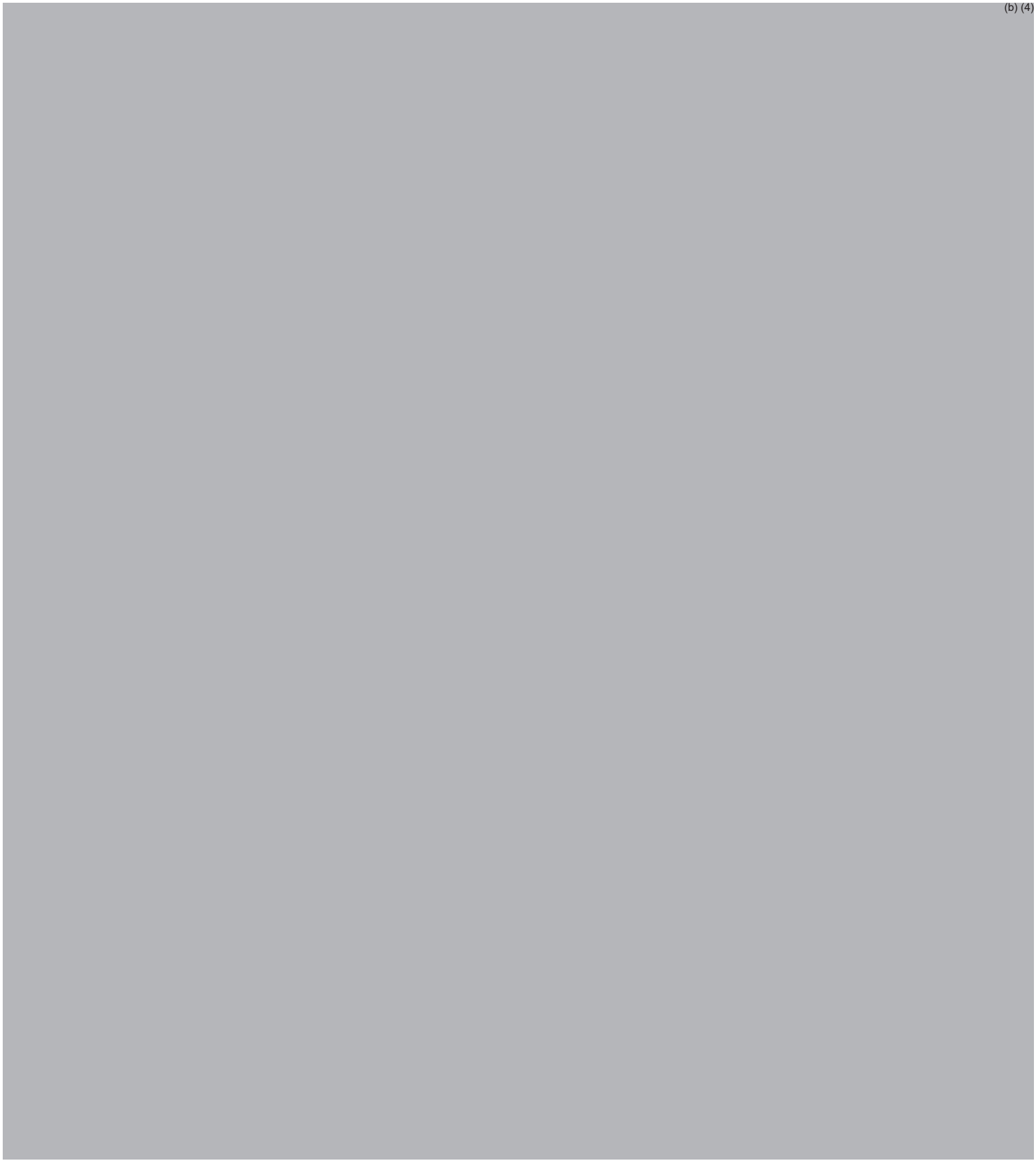


7.3.Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608 (Needle-based injection systems for medical use - requirements and test methods; Part 1: Needle-based injection systems, and Part 5: Automated functions)	**Y**	**Y**
ISO 23908-1 (Sharps injury protection - Requirements and test methods - Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling)	**Y**	**Y**

7.4.Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The Design Control Review appears adequate		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8. RISK ANALYSIS

8.1.Risk Management Plan

Reviewer Comments

In each submission, section 3.2.R Regional Information, risk Management Information (Seq0074 and 0079), the Sponsor provided a summary of the risk management plan of the NSP-PFS and AI.
They state:
AbbVie created a risk management plan which outlines the approaches and activities for identifying the hazards and associated risks, establishing and evaluating the resulting risks, controlling the risks as necessary and monitoring the effectiveness of the controls over the entire lifecycle of the product.

All risk management documentation is stored in the risk management file (RMF). Ongoing maintenance of the RMF will continue throughout the product lifecycle. Items considered for impact to the RMF include but are not limited to:

process or design changes, periodic product reviews, the identification of new hazards, a change in occurrence of an existing hazard, and changes (new, modified, or obsolete) to modes of control. Reviews of risk management activities are integrated into the design control process according to established AbbVie procedures.

A System Risk Assessment (SRA) was provided for each device (NSP-PFS and AI) which contains the key columns of data. The full system risk assessment is stored in the design history file for the project; howver the mitigations for the hazardous situations are presented and risk is defined by the following scale presented in sequence 0001.

- The risks were rated as low if the SxPOH score is 1-8.
- The risks were rated at medium if the SxPOH score is 9-12.
- The risks were rated as high if the SxPOH score is 13-25.

Figure 1. Risk Acceptability Table

Risk Acceptability	Occurrence				
Severity	1	2	3	4	5
5	5	10	15	20	25
4	4	8	12	16	20
3	3	6	9	12	15
2	2	4	6	8	10
1	1	2	3	4	5

Risk was scaled using the following table

Medical Severity Rating Scale

- 1 (patient inconvenience, no safety risk)
- 2 (minor)
- 3 (moderate)
- 4 (high)
- 5 (death or life threatening injury).

The general methodology grading of risk is aligned with ISO 14971:

The risk management plan is similar in wording for both devices and acceptable.

8.2.Hazard Analysis and Risk Summary Report

Reviewer Comments

The system level risk assessment included identification of hazards, hazardous situations and sequence of events; estimation and evaluation of severity of harm, occurrence of harm and risk acceptability; plus the determination and implementation of risk controls. A Use Error Risk Analysis (UERA), Design Failure Mode and Effect Analyses (dFMEA), and Process Failure Mode and Effect Analyses (pFMEA) were created and used to influence system level risk estimates and to further analyze hazard causes as needed.

For the NSP-PFS, the residual risk levels demonstrated no high risks and a combination of medium and low risks. A benefit risk statement deemed the results acceptable based on the history of PFS used in delivery of medicinal products and the use of the NSP-PFS in the original approved BLA.

For the AI, per the sponsor, the residual risk levels demonstrate no high risks, three medium risks, and the remaining are low risks. The probability of occurrence of these harms have been reduced as far as possible through the implemented risk controls.
The overall risk for the AI for use is considered acceptable and from this evaluation, the benefits of using the AI outweigh the risks identified.

Note: The original Hazard Analysis for the NSP-PFS was provided in seq0001 3.2R Regional Information, Risk Management Information.
SRA – system risk analysis were provided for each combination product presentation which provide a high level review of the risk analysis.

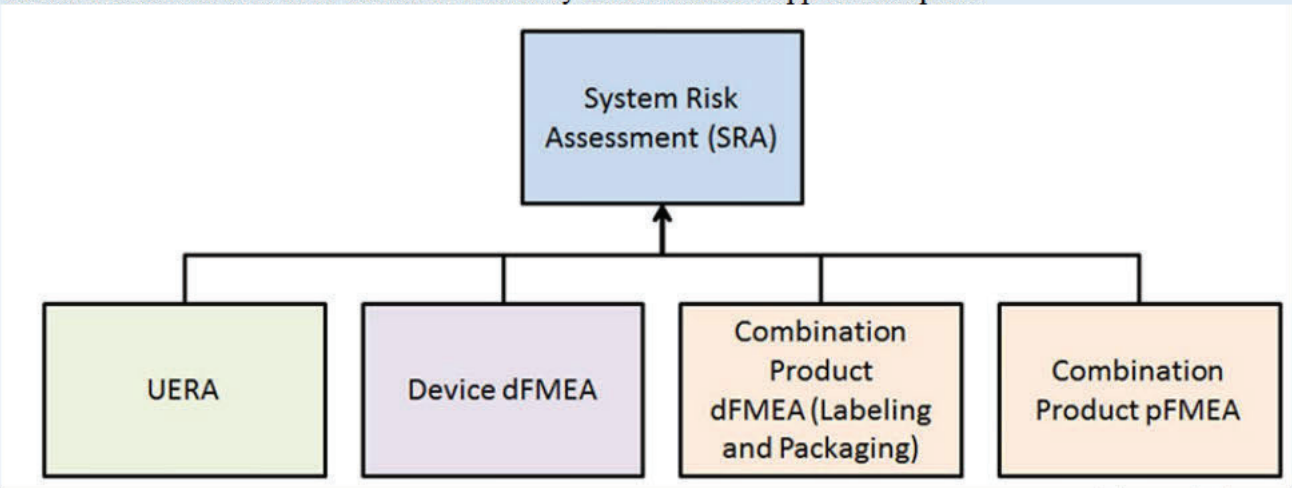
8.3.Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☐ Yes ☐ No ☐ N/A	☑ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☐ N/A

Reviewer Comments
Risk Analysis appears adequate.

It is unclear from the SRA how the risk ratings are determined from the calculation of Severity and Probability of Occurrence. It is also unclear what the P1 and P2 Residual columns represent.
Also, Need the Full system risk assessment including A Use Error Risk Analysis (UERA), Design Failure Mode and Effect Analyses (dFMEA), and Process Failure Mode and Effect Analyses (pFMEA) for each presentation for review.
Resolved IR#1 received 2/18/21, explanation provided. P1 and P2 are used to ultimately determine the Probability of Harm (occurrence) in the formula Risk= Severity x Occurrence. Risk documentation was provided including all documents as shown in their document hierarchy below and each appears adequate.



CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

Follow-On Deficiency	Date Sent: 2/3/2021	Date/Sequence Received: 2/18/2021

Information Request #1

While you provided System Risk Analysis Tables for the NSP-PFS and AI presentations of your drug product which identifies the hazards, hazardous situations, and harms related to your device, it is unclear how the risk level is determined. Please clarify what the columns of P1-Residual and P2-Residual represent and how the calculation of risk is determined using these columns. Also please provide the full system risk assessments for both the NSP-PFS and AI, including DFMEA, PFMEA and UFMEA for review to demonstrate risk has been mitigated to an acceptable level.

Sponsor Response

AbbVie has described the system risk management process in Section 3.2.P.2.4 Container Closure System, Chapter 3.2. Additional information for the system risk assessment is located in Section 3.2. R Regional Information - System Risk Assessment. Further details on how the risk level is determined, what the P1-residual and P2-residual columns represent and how the risk is calculated and evaluated, are provided below. The requested risk assessment documents for the NSP-PFS (Table 14) and AI (Table 15) are provided with this response in Module 3, Section 3.2.R.

The risk evaluation and acceptance criteria are defined. P1 is the probability of the occurrence of exposure to the Hazard (otherwise known as the Hazardous Situation) see Table 7. If the event doesn't result in patient harm, the risk level will be considered low

7. Probability of Occurrence of Exposure to the Hazard

P1	Probability of Occurrence of Exposure to the Hazard	
Occurrence Level	**Qualitative**	**Example Quantitative Range**
Frequent 5	Exposure to the specified hazard has occurred and/or is likely to occur regularly or many times during the life of the product given the identified sequences of events (SOEs)	$1 \geq x > 1x10^{-1}$
Probable 4	Exposure to the specified hazard has occurred and/or is likely to occur several times during the life of the product given the identified SOEs.	$1x10^{-1} \geq x > 1x10^{-2}$
Occasional 3	Exposure to the specified hazard occurred and/or will occur infrequently during the life of the product given the identified SOEs	$1x10^{-2} \geq x > 1x10^{-3}$
Remote 2	Exposure to the specified hazard situation has occurred and/or will rarely occur during the life of the product given the identified SOEs.	$1x10^{-3} \geq x > 1x10^{-4}$
Improbable 1	Exposure to the specified hazard has not occurred and/or is not expected to occur during the life of the product given the identified SOEs.	$1x10^{-4} \geq x > 0$

P2 is the probability of occurrence that the hazardous situation will result in a harm, see Table 8.

Table 8. Probability of Occurrence of the Hazardous Situation resulting in Harm

P2	Probability of Occurrence of the Hazardous Situation resulting in Harm	
Occurrence Level	**Qualitative**	**Example Quantitative Range**
Frequent 5	The specified harm has occurred and/or is likely to occur regularly or many times with consideration of the likelihood of the hazardous situation	$1 \geq x > 1x10^{-1}$
Probable 4	The specified harm has occurred and/or is likely to occur several times with consideration of the likelihood of the hazardous situation.	$1x10^{-1} \geq x > 1x10^{-2}$
Occasional 3	The specified harm has occurred and/or will occur infrequently with consideration of the likelihood of the hazardous situation.	$1x10^{-2} \geq x > 1x10^{-3}$
Remote 2	The specified harm has occurred and/or will rarely occur with consideration of the likelihood of the hazardous situation.	$1x10^{-3} \geq x > 1x10^{-4}$
Improbable 1	The specified harm has not occurred and/or is not expected to occur with consideration of the likelihood of the hazardous situation.	$1x10^{-4} \geq x > 0$

P1 and P2 are used in the following matrix to define the probability of harm (PoH), see Table 9.

Table 9. Probability of Harm Matrix

	PoH (5x5 Matrix)					
P1	**Frequent**	Improbable (1)	Remote (2)	Occasional (3)	Probable (4)	Frequent (5)
	Probable	Improbable (1)	Improbable (1)	Remote (2)	Occasional (3)	Probable (4)
	Occasional	Improbable (1)	Improbable (1)	Improbable (1)	Remote (2)	Occasional (3)
	Remote	Improbable (1)	Improbable (1)	Improbable (1)	Improbable (1)	Remote (2)
	Improbable	Improbable (1)	Improbable (1)	Improbable (1)	Improbable (1)	Improbable (1)
		Improbable	**Remote**	**Occasional**	**Probable**	**Frequent**
		P2				

In addition, the

Reviewer Comments	The explanation of the P1 and P2 variables was adequate and all risk analysis documentation was provided as requested
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9. DESIGN VERIFICATION REVIEW

9.1.Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

9.1.1.1. NSP-PFS Verification:

Design Input	Design Output	Verification Method	Results/Deviations	Stability (Y/N)	Validated through Clinical, Human Factors or Other	Shipping (Y/N)
Protect the user from accidental needle stick injury	The NSP-PFS must be fully activated at the end of injection stroke.	Yes visual inspection of deployment and subsequent lock of needle guard. (P/F) 93 samples (attribute) (97.5%/90%)*** (changed to 99%/95% on 3/23/21)	Compliance in each environment standard, warm, cool, vibration, simulated shipping	Y	Y 5.3.5.4 human factors report	Y
	Needle Cover Override Force ≥ (b) (4)	Verified by (b) (4) per ISO 23908 (K123743)	Compliance per subcomponent CofA	N/A	Y 5.3.5.4 human factors report *see note	N/A
	Maximum force on plunger rod for ejection and actuation ≤ (b) (4)	Yes, max force measured to expel the PFS contents and activate NS trigger mechanism at end of stroke (P/F, attribute 45 samples (95%/90%)*** (changed to 99%/95% on 3/23/21)	Compliance in each environment standard, warm, cool, vibration, simulated shipping	Y	Y 5.3.5.4 human factors report *see note	Y

	Guard must enclose needle and prevent finger access per ISO 23908	[redacted] d/validated by stackup analysis per ISO 23908 – (K123743)	Compliance per subcomponent CofA	N/A	Y 5.3.5.4 human factors report	N/A

EPR's are bolded

*NOTE: The sponsor referred to simulated use testing and HF as validation of their specifications. This information is not adequate to validate their specifications aside from dose accuracy and needle length since the devices used in simulated use and clinical studies would not perform at the specification limits only the nominal. However, a review of the proposed specifications for Needle override force and maximum force on plunger for ejection and activation (including breakloose force and glide force), even considering the test speed are adequate compared to other marketed products.

***NOTE: per Sponsor Response to IR#3 received 3/23/21, for the NSP-PFS testing (which is assessed using an attribute data verification approach), pooling the data from all test conditions for the activation of the USPP and maximum force on the plunger rod, test yields >299 samples, exceeding the quantity needed to demonstrate 99% reliability. All samples tested passed (see individual tests methods described below)

Reviewer Comment

Based on current best review practices performance of the PFS devices, only the NSD will require review for device performance (needle safety activation, lockout, preactivation/drop testing, etc.), within FDA Guidance: Medical Devices with Sharps Injury Prevention Features (https://www.fda.gov/media/71142/download) and ISO 23908.

Test atmospheres include standard, warm, and cool as identified per ISO 11608-1.
In addition, preconditionings included vibration and free-fall per ISO 11608-1 and simulated shipment was based on ASTM-D999 and ASTM-D4169.
Storage conditions and the test intervals were based on ICH guidelines comprising the following conditions and durations: 5°C for 24 months (recommended storage condition), 25°C/60% RH for six months (accelerated condition) and 40°C/75% RH for three months (stressed condition).

3.2.P.5.1 Specifications NSP-PFS, per the sponsor:

Design Verification [redacted] similar to approved approach of original BLA with NSP-PFS (75 mg/0.83 mL))
The NSP components (USPP, PR and AFF) are commercially available products that are purchased [redacted] AbbVie is used design verification studies conducted by [redacted] to meet design verification activities specific to the NSP. AbbVie assessed the suitability and acceptability of the [redacted] studies based on documents and certificates provided by [redacted] has verified the functionality of the NSP with a 1 mL long syringe throughout shelf-life and controls the USPP, PR and AFF functionality at components release. The same components are used on the NSP-PFS of the original submission and the same verification justification was used.

The sponsor does not provide the design verification reports. While they provide a summary of the test method validation approach which has the test methods this information is insufficient in determining if the testing was carried out adequately. Please also explain your sample sizes in relation to reliability limits. Resolved IR#1 received 2/18/21, all design verification testing documentation provided as well as explaination into sample sizes and reliability limits.

Title:	RISA-PFS-060-873 - Activation of USPP The NSP-PFS must be fully activated at the end of injection stroke after (pre)conditioning condition
Scope/Objective & Acceptance Criteria:	*The USPP must be fully activated by the end of the ejection stroke (needle guard fully deployed and locked).*
Methods	*Testing of activation and lock of USPP according toP-500704-E-B (applicable parts only)*
Results:	For each pre-condition, standard, warm, vibration, shipping
Conclusions/ Reviewer Comments:	***The Reliability for needle stick prevention should be 99%. Currently it is 97.5% for this verification method related to design output for needle stick prevention We recommend that reliability of 99% as a baseline for any attribute testing related to needle stick prevention based on the identified risk of "infection" from an unintentional needle stick per the FDA guidance document "Guidance for Industry and FDA Staff - Medical Devices with Sharps Injury Prevention Features" (https://www.fda.gov/files/medical%20devices/published/Medical-Devices-withSharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff- %28PDF%29.pdf). – see IR #3 sent 3/18/21. Resolved Per response to IR#3 received 3/23/21. For testing to determine that the The NSP-PFS must be fully activated by the end of the ejection stroke, which is assessed using an attribute data verification approach, pooling the data from all test conditions for the activation of the USPP test yields 651 samples, exceeding the quantity needed to demonstrate 99% reliability. All samples tested passed.
Acceptable:	☒Yes ☐No

PR RISA-PFS-060-183 - Activation	P-500704-E-B	USPP must be fully activated by end of ejection stroke; needle is completely enclosed by the USPP device	93	Zero defect	N/A	Pass

Title:	RISA-PFS-060-875 - Ejection force test Testing of maximum force during ejection after (pre)conditioning condition

Scope/Objective & Acceptance Criteria:	*No more than* (b) (4) *at a velocity of* (b) (4) *throughout ejection P/F*
Methods	*Testing according to P-500705-E-B and P-500705-EB_attachment 01. Attribute testing.*
Results:	For each pre-condition, standard, warm, vibration, shipping

RISA-PFS-060-185 - Ejection Force	P-500705-E-B P-500705-E-B_A01 *)	attribute testing: evaluation pass/fail The maximum force on the plunger rod during ejection must not be more than (b) (4) measured at nominal velocity of at least (b) (4) The activation force (in combination with concurrent extrusion forces) must not be more than 20N measured at nominal velocity of at	45	Zero defect	N/A	Pass

Conclusions/ Reviewer Comments:	The Reliability for needle stick prevention should be 99%. Currently it is 95% for this verification method related to design output for needle stick prevention We recommend that reliability of 99% as a baseline for any attribute testing related to needle stick prevention based on the identified risk of "infection" from an unintentional needle stick per the FDA guidance document "Guidance for Industry and FDA Staff - Medical Devices with Sharps Injury Prevention Features" (https://www.fda.gov/files/medical%20devices/published/Medical-Devices-withSharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff- %28PDF%29.pdf). – see IR #3 sent 3/18/21. Resolved Per IR#3 response received 3/23/21. For The maximum force on the plunger rod for ejection and activation must not be more than (b) (4) for the NSP-PFS (which is assessed using an attribute data verification approach), pooling the data from all test conditions for the ejection and activation of the NSP test yields 315 samples, exceeding the quantity needed to demonstrate 99% reliability. All samples tested passed
Acceptable:	☒Yes ☐No

9.1.1.2. AI Verification:

AI Verification
Results from Sequence 079, 3.2.P.2.4 Container Closure System, 6.3.1 Table 7 (standard atmosphere)

Design Input	Design Output	Verification Method	Results/Deviations	Stability (Y/N)	Validated through Clinical, Human Factors or Other	Shipping (Y/N)
Total axial force to remove the RNS remover cover and syringe RNS from the combination product	RNS remover cover and syringe RNS removal force (b) (4)	Maximum force measurement to pull off RNS remover cover (Axial direction)	6.3.1 Table 7 Mean =14N, SD = 1.1N 30 samples, 90%/95%	Y	Clinical Study M16-005, Human Factors	Y
AI Needle Shield Protection Under Compression	needle protection not compromised under force (b) (4)	Force measurement (side force, top force, and compression tested).	Complies with each 91 samples, attribute 97.5%/90%%)*** (changed to 99%/95% on 3/23/21)	Y	Clinical Study M16-005, Human Factors	Y
Dose Accuracy (extractable volume)	(b) (4) L	Weight measurement	Mean = 1.0ml, SD =0.00mL 60 samples, 95%/95%	Y	Clinical Study M16-005, Human Factors	Y
Needle Shield Retraction Force	(b) (4)	Maximum force measurement pushing the AI needle shield to retract it(axial direction)	Mean = 4.8N, SD = 0.05N 30 samples, 90%/95%	Y	Clinical Study M16-005, Human Factors	Y
Activation Force	(b) (4)	Maximum force measurement to actuate the trigger button.	Mean = 9N, SD = 0.5N 30 samples, 90%/95%	Y	Clinical Study M16-005, Human Factors	Y
Injection Time	≤15 seconds**	timed measurement - time from actuation of the trigger button to the end of stopper movement is recorded manually using a stop watch	Mean = 5s, SD = 0.4s 30 samples, 90%/95%	Y	Clinical Study M16-005, Human Factors	Y

Extended Needle Length	(b) (4)	Depth measurement	Mean = 7.7mm, SD = 0.15mm 77 samples, 95%/95%	Y	Clinical Study M16-005, Human Factors	Y
Yellow plunger rod function	After volume ejection of the autoinjector, the yellow plunger rod fills the window	Visual inspection of yellow indicator filling window after injection.	Complies 45 samples, 95%/90%	Y	Clinical Study M16-005, Human Factors	Y
Actuation	The autoinjector can be actuated by pressing the trigger button with the AI needle shield retracted. Audible click at activation and at the end of the ejection. Visual control of the start (movment of the start stopper) and end of the ejection (movement end stopper / plunger rod movement).	Visual check at start of actuation. Audible checks at start and end of delivery.	Complies 45 samples, 95%/90%	Y	Clinical Study M16-005, Human Factors	Y

*NOTE: The sponsor referred to simulated use testing and HF as validation of their specifications. This information is not adequate to validate their specifications aside from dose accuracy and needle length since the devices used in simulated use and clinical studies would not perform at the specification limits only the nominal. However, a review of the proposed specifications for Needle override force and maximum force on plunger for ejection and activation (including breakloose force and glide force), even considering the test speed are adequate compared to other marketed products.

**NOTE: Related to 15s injection time, a formative study with patients was conducted following a simulated use testing approach specific to the AI Hold time task. The primary goal of this study was to assess the extent to which participants were able to complete injections using several autoinjectors, each with different injections times of either 10, 15, or 20 seconds. 36 participants each used (2) pens of different injection times. The first injection trial was "untrained" and (2) failures of complete injection occurred (10s an d15s hold time) out of 36 injections. The second injection trial "trained" had no failures. Participants reported high levels of confidence in completing a full dose of medication (SEQ0079-3.2..P.2 Pharmaceutical Development, Container Closure System AI, 7.4.1 AI Hold time).

***NOTE: per Sponsor Response to IR#3 received 3/23/21, the ability of the AI to resist forces is tested by the accidental needle shield protection force test. (b) (4) The product requirement is

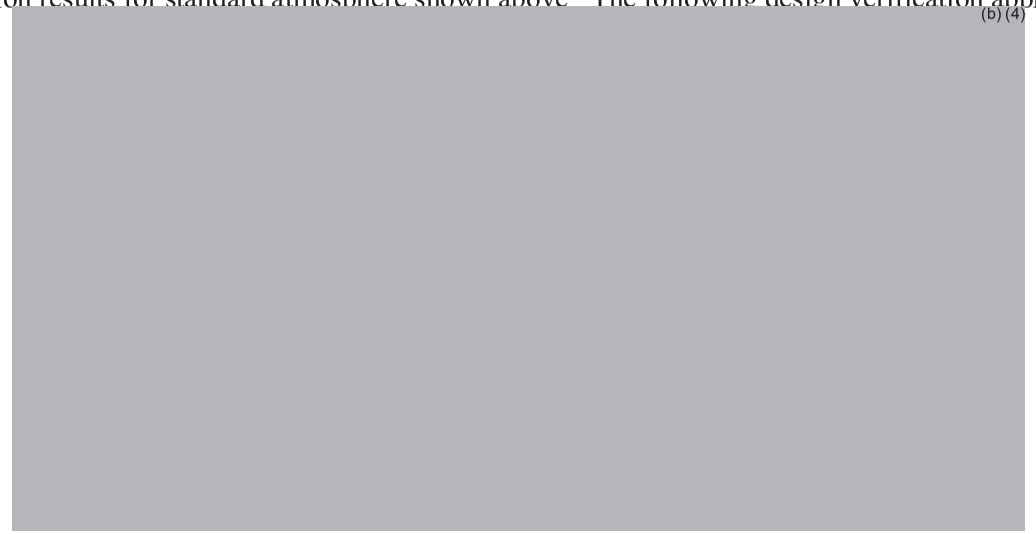
assessed as a pass/fail attribute and the design verification shows the result at each test condition. For this testing, which is assessed using an attribute data verification approach, aggregating the data from all test conditions and preconditioning in each of the three orientation yields 819 samples, exceeding the quantity needed to demonstrate 99% reliability.

Reviewer Comment

Verifications were done at all preconditions in The pre-conditionings of the materials were done per ISO 11608-1 except for shipping conditioning which was performed per ASTM D4169: Standard Practice for Performance Testing of Shipping Containers and Systems and accelerated aging conditioning which was performed per ASTM F1980.

Design verification testing of the AI was conducted using production equivalent components and sub-assemblies using the drug product. The final assembly of the AI (including the drug product used for design verification was conducted under controlled conditions using a process that follows the identical assembly sequence used for commercial production.

Verification results for standard atmosphere shown above. The following design verification approach was utilized, see figure 14.



The following submissions tables each presented similarly acceptable verification results.

Table 8	Summary of DVT Results for AI built with non-conditioned Sub-assemblies and Components: Warm Atmosphere (continued)
Table 9	Summary of DVT Results for AI built with non-conditioned Sub-assemblies and Components: Cool Atmosphere
Table 10	Summary of DVT Results at Standard Atmosphere: AI built with Sub-assemblies and Components pre-conditioned at Cold and Dry Heat Storage

Table 11	Summary of DVT Results at Standard Atmosphere: AI pre-conditioned at Vibration Conditioning
Table 12	Summary of DVT Results at Standard Atmosphere: AI pre-conditioned at Simulated Shipping Conditioning
Table 13	Summary of DVT Results at Standard Atmosphere: AI pre-conditioned at Free-Fall Conditioning

Preconditionings are as follows in Table 3.

Table 3. Overview of Pre-Conditionings

Cold Storage and Dry Heat	(b) (4)
Vibration	
Free-Fall	
Simulated Shipment of the Packaged AI	
Simulated Shipment of the Sub-assemblies and Components	

Accelerated Aging	(b) (4)

Table 4. Overview of Test Atmospheres

Standard	The AI is exposed to a temperature of 23 ± 5°C with a relative humidity of 50 ± 25% for a minimum of 4 hours before execution of the verification test per ISO-11608-1 *Needle-based injection systems for medical use - Requirements and test methods - Part 1: Needle-based injection systems.*
Cool	The AI is subjected to a temperature of 5 ± 3°C (no humidity requirement) for a minimum of 4 hours per ISO-11608-1 *Needle-based injection systems for medical use - Requirements and test methods - Part 1: Needle-based injection systems.* The verification tests were conducted in or immediately after removal from the refrigerated environment except the dose accuracy (delivered volume) test will be conducted in a refrigerated test chamber.
Warm	The AI is subjected to a temperature of 40 ± 2°C with a relative humidity of 50 ± 10% for a minimum of 4 hours per ISO-11608-1 *Needle-based injection systems for medical use - Requirements and test methods - Part 1: Needle-based injection systems.* The verification tests were conducted in or immediately after removal from the warm environment except the dose accuracy (delivered volume) test will be conducted in a warm test chamber.

Formative and summative validation human factors testing was completed with a representative intended user population, performing simulated use administration tasks in a realistic environment. The summative study was conducted to validate safe and effective use of this product. The summative study results indicate that the product configuration including the packaging and instructions are safe and effective for the intended users, uses, and use environments.

The sponsor does not provide the design verification reports. While they provide a summary of the test method validation approach which has the test methods this information is insufficient in determining if the testing was carried out adequately. Please also explain your sample sizes in relation to reliability limits.
Resolved IR#1 received 2/18/21, all design verification testing documentation provided as well as explaination into sample sizes and reliability limits.

9.1.2. *Evaluation of Test Methods*

Title:	**Total Axial Force to remove the RNS remover cover and syring RS from the combination product**
Scope/Objective & Acceptance Criteria:	RNS remover cover and syringe RNS removal force force (b) (4)
Methods	Maximum force measurement to pull off RNS remover cover (Axial direction) *No pre-conditioning (Test atmosphere (warm, cool)),* *Pre-conditioning: Hot/Cold, Vibration , Simulated Shipping Study, Free-fall, Acc Aging Study Arm 1, Acc Aging Study Arm 2*
Results:	N=30, N=77(cool atmosphere, non normally distributed data), pass under all conditions
Conclusions/ Reviewer Comments:	Testing is adequate, 95%/95%
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Title:	**AI needle shield protection under compression**
Scope/Objective & Acceptance Criteria:	needle protection not compromised under force (b) (4)
Methods	(b) (4)
	No pre-conditioning (Test atmosphere (warm, cool)),

	Pre-conditioning: Hot/Cold, Vibration , Simulated Shipping Study, Free-fall, Acc Aging Study Arm 1, Acc Aging Study Arm 2
Results:	N=91, pass under all conditions
Conclusions/ Reviewer Comments:	***The Reliability for needle stick prevention should be 99%. Currently it is 97.5% for this verification method related to design output for needle stick prevention We recommend that reliability of 99% as a baseline for any attribute testing related to needle stick prevention based on the identified risk of "infection" from an unintentional needle stick per the FDA guidance document "Guidance for Industry and FDA Staff - Medical Devices with Sharps Injury Prevention Features" (https://www.fda.gov/files/medical%20devices/published/Medical-Devices-withSharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff- %28PDF%29.pdf). – see IR #3 sent 3/18/21. Resolved Per response to IR#3 received 3/23/21, the ability of the AI to resist forces is tested by the accidental needle shield protection force test. Needle shield protection force is tested in three orientations: in compression, from the top of the AI and from the side of the AI. The product requirement is assessed as a pass/fail attribute and the design verification shows the result at each test condition. For this testing, which is assessed using an attribute data verification approach, aggregating the data from all test conditions and preconditioning in each of the three orientation yields 819 samples, exceeding the quantity needed to demonstrate 99% reliability.
Acceptable:	☒Yes ☐No

Title:	**Dose Accuracy (extractable volume)**
Scope/Objective & Acceptance Criteria:	(b) (4)
Methods	(b) (4) *Pre-conditioning: Hot/Cold, Vibration , Simulated Shipping Study, Free-fall, Acc Aging Study Arm 1, Acc Aging Study Arm 2* *Accelerated aging to 2 years (stated shelf life of combination product) (see table 3 Overview of Pre-conditionings above)*
Results:	N=60, pass under all conditions
Conclusions/ Reviewer Comments:	Testing is adequate, 95%/97.5%

Acceptable:	☒Yes ☐No

Title:	**Needle shield retraction force**
Scope/Objective & Acceptance Criteria:	(b) (4)
Methods	(b) (4) *No pre-conditioning (Test atmosphere (warm, cool)),* *Pre-conditioning: Hot/Cold, Vibration , Simulated Shipping Study, Free-fall, Acc Aging Study Arm 1, Acc Aging Study Arm 2*
Results:	N=30, N=77(cool atmosphere, non normally distributed data), pass under all conditions
Conclusions/ Reviewer Comments**:**	Testing is adequate, 95%/95%
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Title:	**Activation force**
Scope/Objective & Acceptance Criteria:	(b) (4)
Methods	(b) (4) *No pre-conditioning (Test atmosphere (warm, cool)),* *Pre-conditioning: Hot/Cold, Vibration , Simulated Shipping Study, Free-fall, Acc Aging Study Arm 1, Acc Aging Study Arm 2*
Results:	N=30, pass under all conditions
Conclusions/ Reviewer Comments**:**	Testing is adequate, 95%/95%
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Title:	**Injection Time**
Scope/Objective & Acceptance Criteria:	≤15 seconds
Methods	timed measurement - time from actuation of the trigger button to the end of stopper movement is recorded manually using a stop watch *No pre-conditioning (Test atmosphere (warm, cool)),* *Pre-conditioning: Hot/Cold, Vibration , Simulated Shipping Study, Free-fall, Acc Aging Study Arm 2*
Results:	N=30, pass under all conditions
Conclusions/ Reviewer Comments**:**	Testing is adequate, 95%/95% Related to 15s injection time, a formative study with patients was conducted following a simulated use testing approach specific to the AI Hold time task. The primary goal of this study was to assess the extent to which participants were able to complete injections using several autoinjectors, each with different injections times of either 10, 15, or 20 seconds. 36 participants each used (2) pens of different injection times. The first injection trial was "untrained" and (2) failures of complete injection occurred (10s an d15s hold time) out of 36 injections. The second injection trial "trained" had no failures. Participants reported high levels of confidence in completing a full dose of medication (SEQ0079-3.2..P.2 Pharmaceutical Development, Container Closure System AI, 7.4.1 AI Hold time).
Acceptable:	☒**Yes** ☐**No**

Reviewer Comment
N/A

Title:	Extended needle length
Scope/Objective & Acceptance Criteria:	(b) (4)
Methods	Depth measurement *No pre-conditioning (Test atmosphere (warm, cool)),* *Pre-conditioning: Hot/Cold, Vibration , Simulated Shipping Study, Free-fall, Acc Aging Study Arm 1, Acc Aging Study Arm 2*

Results:	N=77 (non normally distributed data), pass under all conditions
Conclusions/ Reviewer Comments:	Testing is adequate, 95%/95%
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Title:	**Yellow plunger rod function**
Scope/Objective & Acceptance Criteria:	After volume ejection of the autoinjector, the yellow plunger rod fills the window
Methods	Visual inspection of yellow indicator filling window after injection.
Results:	N=45, pass under all conditions
Conclusions/ Reviewer Comments:	Testing is adequate, 95%/90%
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Title:	**Actuation**
Scope/Objective & Acceptance Criteria:	The autoinjector can be actuated by pressing the trigger button with the AI needle shield retracted. Audible click at activation and at the end of the ejection. Visual control of the start (movment of the start stopper) and end of the ejection (movement end stopper / plunger rod movement).
Methods	Visual check at start of actuation. Audible checks at start and end of delivery *No pre-conditioning (Test atmosphere (warm, cool)),* *Pre-conditioning: Hot/Cold, Vibration , Simulated Shipping Study, Free-fall, Acc Aging Study Arm 1, Acc Aging Study Arm 2*
Results:	N=45, pass under all conditions
Conclusions/ Reviewer Comments:	Testing is adequate, 95%/90%

	Note: There is no criteria for he audible/visual feedback, ex. Clicks happen +/- x seconds after end of injection, how loud are the clicks? See IR#3 below
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Insert Additional Design Verification Table

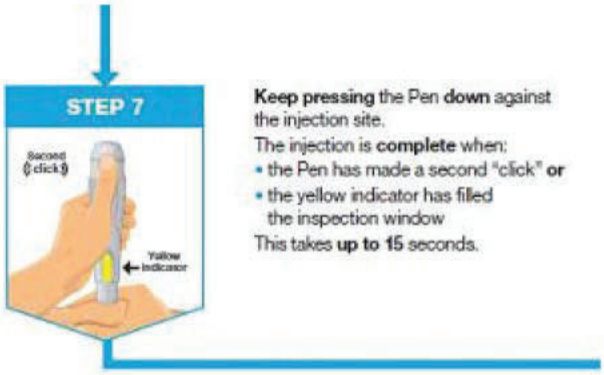
9.2.Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Design Verification is adequate		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: **2/8/2021**	**Date/Sequence Received:** **3/18/2021**
Information Request #1	While you provided a design verification summary for your prefilled syringe and autoinjector, you did not provide the actual design verification reports. The design verification reports are needed to assess how the verification testing was conducted and determine if it was conducted adequately. Provide the prefilled syringe and autoinjector design verification reports including the real time and accelerated aging testing. Ensure that the test reports contain the data collected, including force traces (e.g., injection force), and statistical summary (mean, min, max, standard deviation, graph) for variable data. Also provide the confidence and reliability used for each test performed.	
Sponsor Response	The design verification (DV) protocols, records/reports and raw data documents for the NSP-PFS and the AI are provided with this response in Module 3, Section 3.2.R. See Table 2 for a list of the NSP-PFS documents. See Table 3 for a list of the AI documents. The provided records/reports and raw data documents contain force traces (as applicable) and statistical summary information (mean, min, max, standard deviation) for variable data. For variable data evaluated against statistical requirements the check for normal distribution was evaluated using validated Excel spreadsheets. Information on statistical analysis and normality evaluation is contained in QPP11-02-005-W001 Design Verification Criteria and D-502925 Anderson-Darling Normality Test: Calculation of the p-value with Microsoft Excel, respectively (see Table 4). The confidence and reliability used for the DV tests were defined in the respective DV protocols, which were built in alignment with further reference documents provided with this response in Module 1, Section 1.11.1 Quality Information Amendment, see Table 4.	
Reviewer Comments	The Reliability for needle stick prevention should be 99%. Currently it is 95% to 97.5% for the verification methods related to design output for needle stick prevention We recommend that reliability of 99% as a baseline for any attribute testing related to needle stick prevention based on the identified risk of "infection" from an unintentional needle stick per the FDA guidance document "Guidance for Industry and FDA Staff - Medical Devices with Sharps Injury Prevention Features" (https://www.fda.gov/files/medical%20devices/published/Medical-Devices-withSharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff- %28PDF%29.pdf). – see IR #3 below sent 3/18/21.	
Response Adequate:	☐ **Yes** ☑ **No, See IR #3 Sent on 3/18/2021**	

	Date Sent:	**Date/Sequence Received:**

	3/18/2021	3/23/2021
Information Request #3	1. For both presentations of your combination drug product, the Needle-Stick Prevention Pre-Filled Syringe (NSP-PFS) and the AutoInjector (AI), you provided verification testing of your needle stick prevention attributes. However, the testing results were based on samples sizes which reflect only a 95% to 97.5% reliability reflecting on risk severity levels of "low" as determined from your risk analyses documentation. We recommend that reliability of 99% as a baseline for any attribute testing related to needle stick prevention based on the identified risk of "infection" from an unintentional needle stick per the FDA guidance document "Guidance for Industry and FDA Staff - Medical Devices with Sharps Injury Prevention Features" (https://www.fda.gov/files/medical%20devices/published/Medical-Devices-withSharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff-%28PDF%29.pdf). Therefore, reanalyze your data or perform additional testing as necessary to support 99% reliability related to your needle stick prevention attributes of both presentations of your combination product including "activation at end of injection stroke" and "Maximum force on plunger rod" for the NSP-PFS and "AI Needle shield protection under compression" for the AI. 2. You detail verification testing of your AutoInjector including "Actuation" which uses a visual check for the start of actuation and audible checks at the start and end of delivery. However, there is no detail provided for the verification testing data or acceptance criteria related to this audible feedback (click, timing, correlation with dose delivery) function of your device. Your intended user may solely rely on the audible feedback to indicate end of injection. Therefore, if the click is premature, a wet or incomplete injection could occur. In order to determine whether the design of the audible alarm function is controlled by design and effective, design verification on the volume (i.e., decibels) and timing of the click is necessary. Provide verifiable design input requirements for your audible click timing (+/- seconds from end of injection), volume (i.e., decibels) and residual volume after click (delivered volume remaining in device after audible click).	
Sponsor Response	1. AbbVie has reanalyzed data from design verification testing (DVT) to support 99% reliability related to the needle stick prevention attributes for the NSP-PFS and the AI. For attribute data, aggregating data from multiple test atmospheres and sample preconditioning yielded a sufficient sample size for reanalysis. For variable data, the existing data set was reanalyzed at 99% reliability. The reanalysis of the data sets demonstrates 99% reliability related to the needle stick prevention attributes for both NSP-PFS and AI. See Sequence 0114 for further details. Attribute data from the pre-conditioning and test atmospheres has been aggregated into a larger group to assess the data at higher reliability. Aggregating data from different pre-conditioning and test atmospheres results in a data pool that is more challenging than at standard conditions and is considered an appropriate approach to achieve a higher sample size.	

	• For the "NSP-PFS must be fully activated by the end of the ejection stroke", which is assessed using an attribute data verification approach, pooling the data from all test conditions for the activation of the USPP test yields 651 samples, exceeding the quantity needed to demonstrate 99% reliability. All samples tested passed. • For the "maximum force on the plunger rod for ejection and activation must not be more than (b) (4) which is assessed using an attribute data verification approach, pooling the data from all test conditions for the ejection and activation of the NSP test yields \315 samples, exceeding the quantity needed to demonstrate 99% reliability. All samples tested passed. 2. As stated in their response, AbbVie does not intend to add PRs for audible click timing (+/- seconds from end of injection), volume (i.e., decibels) and residual volume after click (delivered volume remaining in device after audible click). Justification is provided in the sponsor response and is summarized in the bullets below: • Per the AI design (b) (4) (b) (4) • Design Verification testing = successful dose delivery • HF engineering/Usability engineering provides evidence of successful injections, demonstrating that the audible and visual cues are adequate to ensure a user can safely and effectively administer the drug product • The instructions for use (IFU) for the AI provide instruction for the user regarding audible and redundant visual cues as shown below  • Adding a PR on the decibel level of the end of delivery click does not reduce the risk profile of the device per the design and use of the AI
Reviewer Comments	Response to #1 is adequate Response to #2 was discussed in internal meeting with Courtney Evans (TL) and Rumi Young (AD). The end of dose audible click is shown to be dependent on design (b) (4) (b) (4)

	(b) (4) Recommendation for Post Market Commitment (6 months to a year timeframe) to either place added Design Input Requirements around the volume level and the timing of the audible cue or to control the design criteria which these characteristics are dependent on (Critical Design Features)
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9.3.Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

Biocompatibility of AI:

(b) (4)

Table 14. Materials and Components of the AI tested for Biocompatibility

(b) (4)

[redacted]

Based on the contact type and duration type, the Sponsor provides cytotoxicity (C), sensitization (S), and irritation (I) testing to support the biocompatibility of the device.

Cytotoxicity:

testing was conducted in accordance FDA recognized standard 10993-5

Table 15. Summary of Cytotoxicity Tests and Results for AI Skin Contact Materials

Material	Test Method	Biological Reactivity Evaluation			Result of Test
		Positive Control	Negative Control	Test Article	

(b) (4)

[redacted]

This is acceptable.

Sensitization:

Sensitization testing was conducted in accordance FDA recognized standard 10993-10.

Table 17. Summary of Skin Sensitization Tests and Results for AI Skin Contact Materials

Material	Test Method	Reaction Evaluation			Result of Test
		Positive Control	Negative Control	Test Article	
(b) (4)					

This is acceptable.

Irritation:

Irritation testing was conducted in accordance FDA recognized standard 10993-10 *conditions*.

Table 16. Summary of Skin Irritation Tests and Results for AI Skin Contact Materials

Material	Test Method	Skin Reaction Evaluation		Result of Test
		Overall Control Group Mean	Overall Test Group Mean	
(b) (4)				

This is acceptable.

BIOCOMPATIBILTY REVIEW CONCLUSION

The Biocompatibility Documentation is adequate

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review
☐ There are clinical studies for review
This information was obtained from the following **documents**:

Reviewer Comment

NSP-PFS, Per 3.2.P.2.4,
The to-be-marketed version of the combination product is the (b) (4)
(b) (4)
(b) (4)

AbbVie has conducted formative and summative human factors studies with the marketed combination product, 75 mg/0.83 mL NSP-PFS and a supplemental human factors study with the to-be-marketed 150 mg/1.0 mL NSP-PFS. Refer to Section 3.2.P.2.4 Container Closure System for the NSP-PFS, Chapter 7.0, for a summary of the human factors program and Module 5.3.5.4 Other Studies - Human Factors Engineering and Usability Engineering Report for the human factors summary reports. The summative validation and supplemental simulated use studies concluded that the product is safe and effective for the intended users, uses, and use environments.

This approach to validation appears to have been agreed upon during an End of Phase 2 type B meeting (06/24/15) referencing question 23 on page 14 of "150PFS – Correspondence – Meetings" in 1.6 Meetings

Additional Validation Support: NPS-PFS
Consistent with the **FDA advice received on August 16, 2019 and August 22, 2019, no validation study was performed for the risankizumab 150 mg/mL prefilled syringe with NSP**. AbbVie is relying upon the human factors validation study report provided in Module 5, Section 5.3.5.4 in the original BLA 761105 (eCTD Sequence No. 0001) that was submitted on April 23, 2018. Although not required, AbbVie performed a supplemental study for additional information for the risankizumab 150 mg/mL prefilled syringe with NSP to confirm use simplification resulting from 1) user retrieval of one prefilled syringe rather than two prefilled syringes from the carton and 2) the removal of second prefilled syringe injection instructions from the Quick Tips and Instructions for Use.

AI, Per 3.2.P.2.4,
The to-be-marketed version of the combination product was used for the clinical studies:

- M15-990 (ABBV-066) Phase 1 study to evaluate the bioavailability of Risankizumab 150 mg/mL in PFS relative to the 90 mg/mL in the Autoinjector
- M16-005 (ABBV-066) A Multicenter, Single-Arm, Open-Label Study to Assess the Usability of the Risankizumab Autoinjector Combination Product in Adult Patients with Moderate to Severe Plaque Psoriasis

Per the sponsor: To support the registration of the 150 mg/mL risankizumab AI, the following data was agreed to be included in this submission, assuming the PK bridging study (Study M15-990) included a comparison between the 150 mg/mL AI and the 150 mg/mL PFS:

- Human factors studies with the AI (Module 3);

- PK bridging study (Study M15-990) in healthy volunteers comparing the delivery of the AI and PFS;
- A real-life handling study (RLHS) (Study M16-005) that includes assessments of usability, efficacy, safety and tolerability of the self-injection.

*NOTE: The sponsor referred to simulated use testing and clinical study as validation of their specifications. This information is not adequate to validate their specifications aside from dose accuracy and needle length since the devices used in simulated use and clinical studies would not perform at the specification limits only the nominal. However, a review of the proposed specifications for the AI, are adequate compared to other marketed products.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Clinical Validation was not reviewed for this submission.		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☑

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

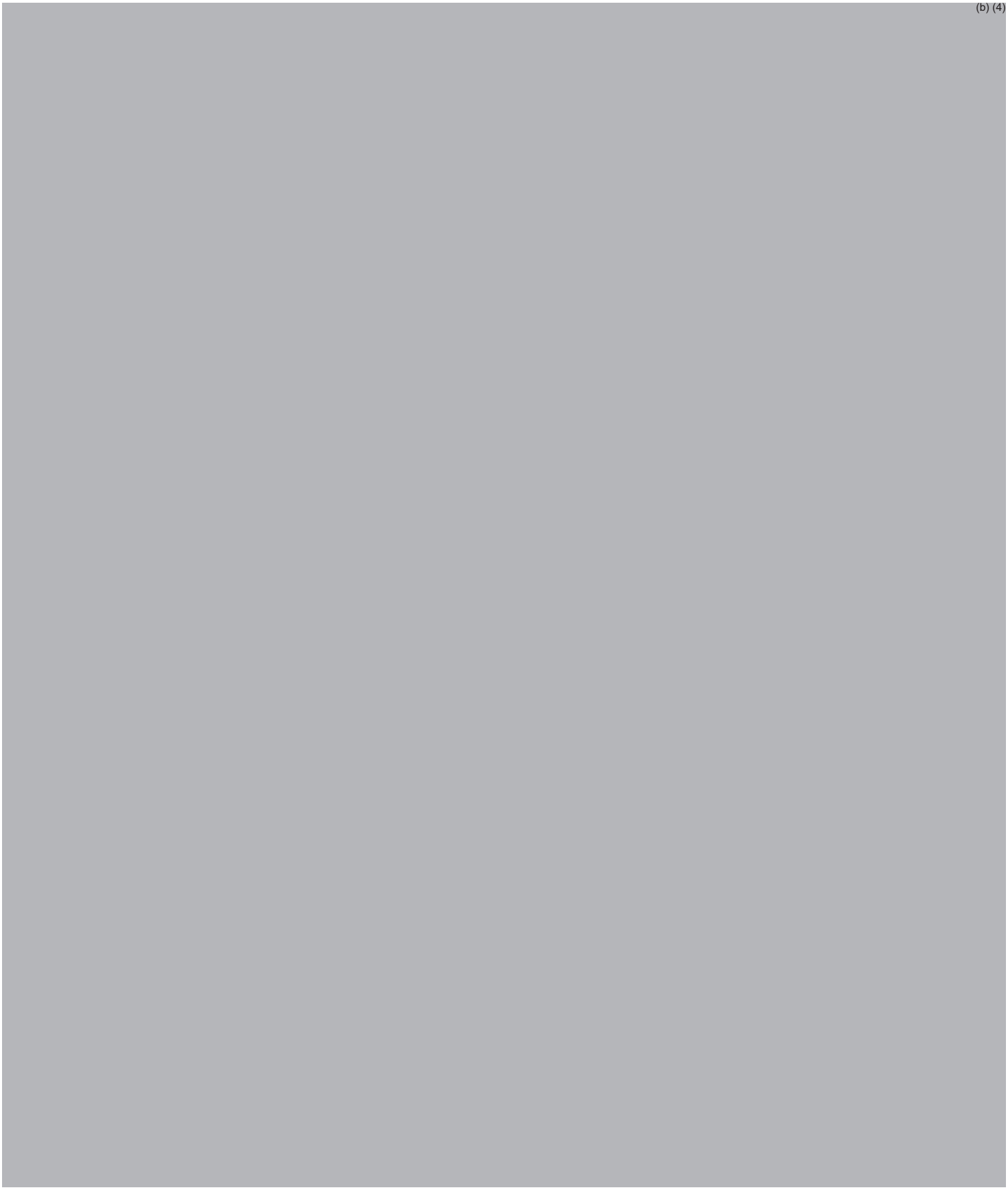
12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

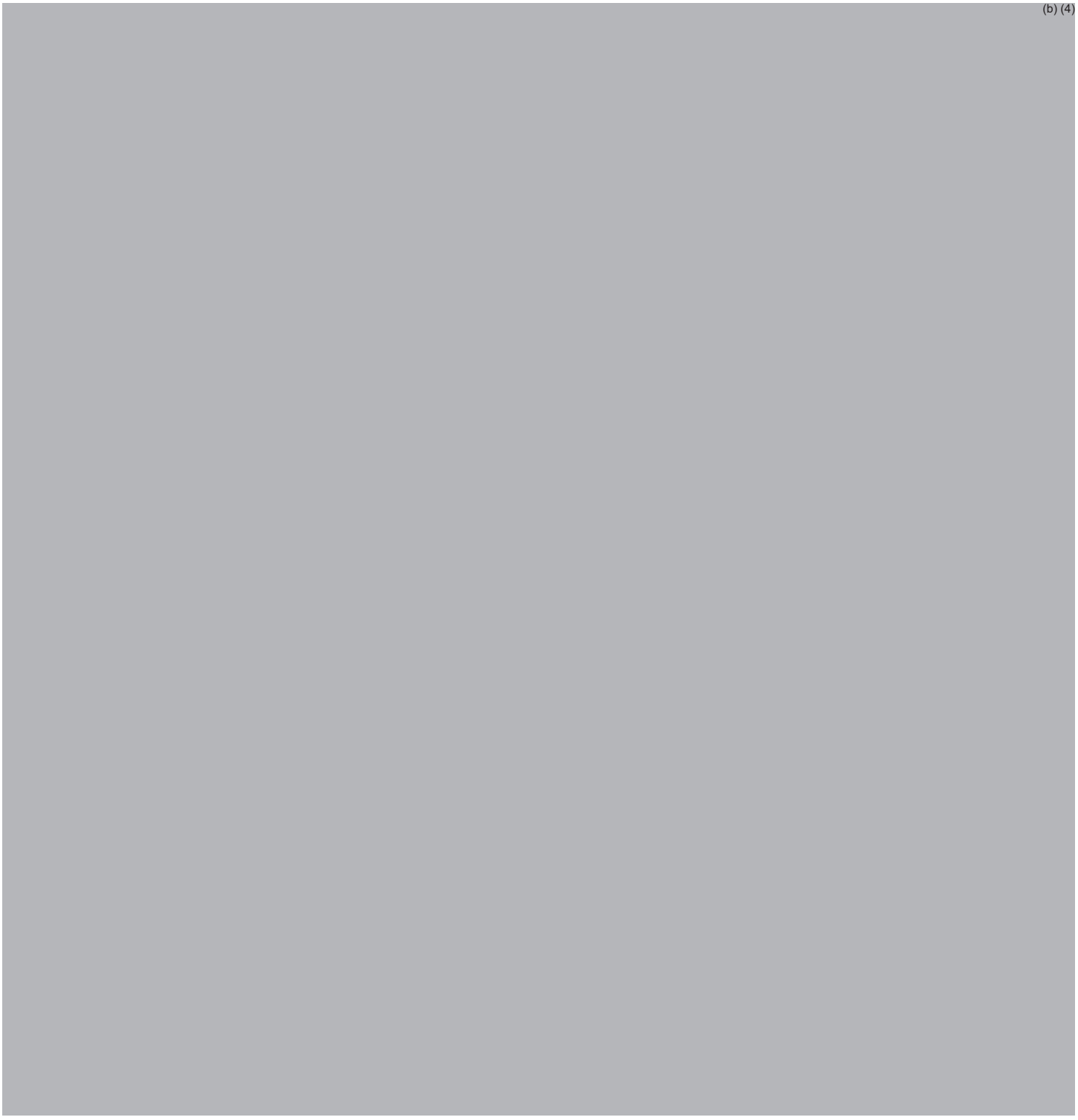
NSP-PFS

(b) (4)



The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

(b) (4)



(b) (4)

[redacted]

Reviewer Comments
Process Validation for NSP-PFS needs to be presented
Resolved IR response of 2/18/21, Process Validations provided including IOQPQ for Assembly and Secondary Packaging and the PPQ at both sites Campoverde and North Chicago.

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☐Yes	☒No

12.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:
☐ Device QSR-based
☑ Drug cGMP-Based Streamline –
☐ Stream-line Both (no streamlined approach)

Quality System information is found in sequence 074, 3.2R Regional Information.

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Abbvie	**Reviewer Discussion** – AbbVie has established procedures for the application of management responsibility to combination products. The procedures define how management with executive responsibility establishes its policy, objective for, and commitment to quality. Management responsibilities start with a commitment to quality as defined by the AbbVie's quality policy. Quality objectives are established, measurable, and consistent with the quality policy. Further, management has established an organizational structure with roles, responsibilities, and authorities that are defined, communicated and implemented throughout the organization.

		The quality council is strategically focused and is responsible for guiding quality across the AbbVie organization. The AbbVie quality council members are the appointed management representatives for each organization. The quality council is accountable to the Chief Executive Officer (CEO). The AbbVie quality council is comprised of the Heads of Quality from each of the following functional quality units: ● Research & Development ● Operations and ● Regulatory Affairs. The foundation of AbbVie's QMS outlines management responsibilities is starting with the AbbVie quality system manual followed by quality policies, operating standards, and procedures in compliance with 21 CFR 820.20 Management Responsibility. QMS requirements, procedures, and records are maintained in validated document management systems. The QMS is audited to assess compliance and effectiveness. Moreover, the management review process is conducted at defined intervals with sufficient frequency to ensure that the quality system is suitable and effective in meeting applicable regulatory standards and quality system requirements. This information adequately fulfills this requirement.
21 CFR 820.30 Summary of Design Controls	Firm(s): Abbvie	**Reviewer Discussion –** AbbVie is accountable for the combination product design controls (e.g., combination product design verification, design validation, drug device interaction testing) and maintains the combination product design history file for the combination product. AbbVie has established procedures for the application of design controls to combination products within the QMS. The procedures define the processes for: Design and Development Planning, Design Input, Design Output and Transfer, Design Review, Design Verification, Design Validation, Design Changes and Design History Files. This information adequately fulfills this requirement.
21 CFR 820.50 Summary of Purchasing Controls	Firm(s):	**Reviewer Discussion –** Supplier control procedures have been established, implemented, and maintained to ensure that services received and/or materials purchased, that can impact regulated product or activity, conform to predefined requirements and quality attributes. (b) (4) (b) (4) This information adequately fulfills this requirement.

21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s):	**Reviewer Discussion** – Reviewed in Section 12.2.3. AbbVie has established procedures for application of corrective and preventive action (CAPA) at facilities involved in the manufacture of the combination product. The procedures outline the process for identifying, initiating, implementing, verifying, and completing CAPAs. A CAPA is created for potential quality problems identified through nonconformances, complaints, returned product, risk assessments, audits, inspections, and trends. Issues are identified and investigated to determine a root cause or contributing cause, if applicable. Corrective and preventive actions are identified and implemented, as needed. Actions are verified and/or validated, as appropriate, to ensure effectiveness and confirm no adverse effect on the finished product. Final approval and CAPA closure represents verification that the corrective and/or preventive actions have been effective. CAPA information is monitored, analyzed, and disseminated for management review

Reviewer Comments

Quality System information is found in sequence 074, 3.2R Regional Information.
The Sponsor provided adequate summary information about the GMP compliance activities

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

12.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	Present
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	Yes
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	Yes, Resolved IR#1 received 2/18/21. CAPA procedures provided.
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	Yes, Resolved IR#1 received 2/18/21.
Investigations into the cause of nonconformities relating to product, processes, and the quality system	Yes
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	Yes
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	Yes
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	Yes, Resolved IR#1 received 2/18/21.

Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	Yes, Resolved IR#1 received 2/18/21.
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	Yes
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	Yes
Requires documentation of all CAPA activities	Yes, Resolved IR#1 received 2/18/21.

Reviewer Comments

The sponsor is missing the elements identified. Their CAPA sop will be requested in IR.
Resolved IR response of 2/18/21, CAPA concerns adequately addressed.

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☐Yes	☒No

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

NSP-PFS

The NSP-PFS control strategy depends on the following:

- The NSP components (USPP, PR and AFF) are commercially available products that are purchased (b) (4) (b) (4)
- AbbVie ensures the quality of the incoming NSP components as defined in Section 3.2.P.7 Container Closure System for the NSP-PFS.
- The PFS is released per tests and acceptance criteria defined in the PFS Section 3.2.P.5.1 Specifications.
- Design verification of the NSP-PFS using PFS assembled per AbbVie's NSP-PFS assembly process confirmed the functionality of NSP-PFS as described in Section 3.2.P.2.4 Container Closure System for the NSP-PFS.
- Test results of the NSP-PFS from ongoing primary stability demonstrate the functionality over the shelf-life at recommended storage conditions as described in Section 3.2.P.8.1 Stability Summary and Conclusions for the NSP-PFS.
- Product quality during final NSP-PFS assembly is controlled by in-process control steps as described in Section 3.2.P.3.3 Manufacturing Steps and Process Controls for the NSP-PFS.
- Final NSP-PFS release and shelf life testing is defined below (Table 1)

Table 1. Specification for the NSP-PFS

Test	Acceptance Criteria	Where applied	
		Release	Shelf-life
Appearance	The assembly of the NSP-PFS is complete, free of damage and without premature activation.	X	X
	The PFS drug product solution can be seen in the viewing window of the NSP-PFS.	X	X
	The PFS label is correctly attached and positioned with text visible.	X	X
	The PFS rotates 360 degrees in at least one direction.	X	X
Functionality	(b) (4)	X	X
		X	X
		X	X
		X	X
Ejection and Activation Force		X	N/A

The Safety Activation Force ≤ (b) (4) (Maximum force on plunger rod for ejection and actuation) is not tested upon release. Resolved per IR#1 received 2/18/21, table above was updated to include Ejection and Activation Force testing at release.

Figure 1. Overview of Commercial Control Strategy Development for the NSP-PFS

(b) (4)

AI

The control strategy for the AI consists of the following elements:

- Testing throughout the development of the AI
- Incoming materials controls for assembly of the AI
- In-process controls in manufacturing/final assembly process to produce the AI with consistent quality
- Release and stability testing as defined in the Specifications section for the AI

Table 1. Specifications for the AI

Test	Acceptance Criteria	Where applied	
		Release	Shelf-life
Appearance	Autoinjector with charcoal grey cover, green trigger button, charcoal grey floating cylinder, and light grey TPE (thermoplastic elastomer) on the body. The autoinjector has a window on each of two diametrically opposed sides through which the pre-filled syringe can be seen. The yellow plunger rod is not visible in the windows.	X	X
Ejection Time	Single values: Not more than 15 s	X	X
Dose Accuracy (Delivered Volume)	Single values: Not less than 1.0 mL	X	X
Yellow Plunger Rod Function	After volume ejection of the autoinjector, the yellow plunger rod fills the window.	X	X
Actuation	The autoinjector can be actuated by pressing the trigger button with the AI needle shield retracted. Audible click at activation and at the end of the ejection. Visual control of the start (movement of the start stopper) and end of the ejection (movement end stopper / plunger rod movement).	X	X
Needle Shield Retraction Force	(b) (4)	X	N/A
Trigger Button Actuation Force		X	N/A

The Needle Shield Retraction Force and Trigger Button Actuation Force is not tested upon release. Resolved per IR#1 received 2/18/21, table above was updated to include both Force testings at release.

Figure 1. Developmental and Commercial Tests and Control Strategy Overview for the AI

(b) (4)

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Essential Performance Requirements Control Strategy NSP-PFS		
Functionality / The NSP-PFS must be fully activated at the end of injection stroke.	Release testing	Y
Needle Cover Override Force (b) (4)	Certificate of Analysis verified for incoming components (this is OK per their justification)	Y
Maximum force on plunger rod for ejection and actuation (b) (4)	PFS release - break out gliding force, requested IR Resolved release testing of NSP-PFS included per IR response of 3/8/21	Y
Guard must enclose needle and prevent finger access per ISO 23908	Certificate of Analysis for incoming components	Y
Essential Performance Requirements Control Strategy AI		
Dose Accuracy (extractable volume) (≥ 1mL)	Release	Y
Activation Force (b) (4)	Sub assy release (requested IR), Resolved release testing of NSP-PFS included per IR response of 3/8/21	Y
Injection Time (≤ 15s)	Release	Y
Needle Shield Retraction Force (b) (4)	Sub assy release (requested IR), Resolved release testing of NSP-PFS included per IR response of 3/8/21	
Extended Needle Length (b) (4)	Product specifications and incoming material acceptance criteria	Y

Reviewer Comments

The Control Strategy for the Essential Performance Requirments is adequate.

Note: Incoming quality testing of the trigger button activation force is performed on front and rear subassembly batches rather than at final drug product lot release.

Paper based evidence such as manufacturer certificates were gathered and evaluated to verify product requirements, where applicable. Furthermore, NSP functionality tests performed by (b) (4) were leveraged, where appropriate, to support the visual and functional design verification testing of the NSP-PFS, see subsection 6.3.2.

No control strategy for the EPRs on the assy line for either presentation. Relying on components CofA and PFS force testing for NSP-PFS, add IR.

For NSP-PFS, (b) (4)

(b) (4)

Resolved IR response #2, 3/8/21- release testing now includes the ejection and actuation (activation) force which will be reported as a single maximum force against a specification of (b) (4) on the final finished NSP-PFS at AbbVie Biotechnology Ltd., Barceloneta, PR and AbbVie Inc. North Chicago, IL.

For AI, verification testing under use conditions of the final finished Auto-Injector (AI) which included Button Activation Force testing and Needle Shield Retraction Force testing but the provided control strategy does not require this EPR testing after the assembly process. Need release controls for the AI EPR's including Button Actuation Force testing and Needle Shield Retraction testing on the final finished AI.

Resolved IR response #2, 3/8/21- release testing now includes the trigger button actuation force which will be reported against a specification of (b) (4) and the needle shield retraction force against a specification of (b) (4) on the final finished AI.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 2/8/2021	**Date/Sequence Received:** 2/18/2021
Information Request #1	**Process Validation** While you presented the Overall Process Validation Acceptance Criteria for your Pre-filled Syringe with Needle Stick Prevention (NSP-PFS) final assembly equipment/process validation, you did not present the results of your qualification, including Installation/Operational Qualification (I/OQ), Performance Qualification (PQ), Process Performance Qualification (PPQ) and Process Validation (PV). Please provide your NSP-PFS process performance qualification results and provide documentation of evidence (summary reports) of both the NSP-PFS and Auto-Injector (AI) line validations. **CAPA Review** You provided a summary review to collectively address requirements for CAPAs; however, the CAPA review did not provide the necessary information. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. Please provide your CAPA SOP and ensure it describes the following: • Review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use. • Statistical analysis of quality data to detect recurring quality problems	

- Procedures for rework, including retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications
- Description of requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems
- Communication of information related to quality problems or nonconforming product to those directly responsible for assuring the quality of such product or the prevention of such problems

Sponsor Response

Process Validation

Production processes for assembly and packaging of the 150 mg/mL NSP-PFS and AI are validated in accordance with AbbVie procedures. The assembly and packaging processes have been validated i.e., IQ/OQ, PQ and PPQ have been completed. PPQ is completed using commercially representative (identical) industrial scale manufacturing equipment and processes and commercially representative commodities using draft, representative label content. The final process confirmation, PV, will be completed with the first-lot-to-stock using the final FDA approved labeling. The summary reports for IOQ/PQ and PPQ are provided with this response in Module 3, Section 3.2.R. See Table 5 for the list of reports for the NSP-PFS and Table 6 for the AI.

Table 5. List of Manufacturing Documents for the NSP-PFS

Document Title	Description
(b) (4)	

CAPA Review

AbbVie recognizes that the questions asked by FDA are taken directly from 21 CFR Parts 820.90 and 820.100. AbbVie built its quality management system based on a review of global regulations, including the applicable 21 CFR parts.

The applicable quality system documents as requested are provided with this response in Module 1, Section 1.11.1 Quality Information Amendment, see Table 1.

a.

AbbVie's corrective action and preventive action (CAPA) policy, QCA01 Corrective Action and Preventive Action Policy, chapter 2.1 states that a corrective action and preventive action system must be established, implemented, and maintained. It must include processes and procedures that define the activities to manage exceptions and will include

- Roles and responsibilities

	● Timeliness requirements ● Evaluation of impact, and ● Required approvals. The review and disposition process for a nonconforming product is described in AbbVie's CAPA procedure QCA01-02-001, Potential/Nonconformity Procedure, chapter 4.6. When "performing containment", the investigator completes the following actions to: ● Determine if the process can continue or should be stopped until appropriate actions have been taken to prevent continuation/ recurrence of the event. ● Segregate or quarantine item(s) under investigation to prevent further use or release. ● Document containment actions taken (inventory quarantine or quality hold). ● Justify where containment is not required. Furthermore, QCA01-02-001-G003 Potential/Nonconformity Resolution Plan Guideline, chapter 2.0, provides: ● Each nonconforming item is addressed with either a correction plan or justification for not correcting an impacted item. Justification for not correcting a nonconforming item includes rationale of why an item in the impact bracket is in fact conforming. At the end of investigation process, CAPA Procedure QCA01-02-001 Potential/Nonconformity Procedure at chapter 9.0 among other requirements, provides to report "batch disposition details" for events involving products. Chapter 10.0 of this same procedure requires the approval of a quality manager or designee, at a minimum. Moreover, QPP01-05-001 Product Certification and Disposition, chapter 3.1, states that QA, when performing a batch certification, ensures (as applicable) that all investigations have been closed, and they support certification. b. Per chapter 2.4 of policy QCA01 Corrective Action and Preventive Action Policy, the CAPA system includes appropriate tracking, review and analysis of data, with sufficient detail to identify trends, using appropriate statistical methodology, where necessary, to allow detection of possible recurring exceptions. Trends may indicate a quality exception and must be evaluated as a potential input to the system. AbbVie's CAPA IT system is the repository for nonconformities. CAPA procedure QCA01-02-001 Potential/Nonconformity Procedure provides instructions for determining frequency of occurrence at chapter 4.9 that is based on a search of the exception report (ER). At minimum, the review period and search criteria have to be justified. Specific instructions on how to perform historic reviews are reported in CAPA guideline QCA01-02-001-R006 Searching and Reporting in the CAPA IT System. The output of the historic reviews can lead to the following event classifications per QCA01-02-001 Potential/Nonconformity Procedure: ● Isolated incident: A frequency of event occurrence of one (1) ● Repeat occurrence: A frequency of event occurrence > 1, but the definition of a trend is not met ● Trend: A sequence or pattern of quality data and information that can be measured and may indicate a potential shift in the quality system. A trend is generally considered a frequency of occurrence of three (3) or more events within the review period. If an event has occurred three or more times, but

will not be considered a trend, justification must be provided in the impact assessment.

Statistical methods are used, as applicable, per chapter 7.5 of QCA01-02-001 Potential/Nonconformity Procedure in order to detect recurring quality issues upon CAPA implementation.

In addition, as part of trend monitoring, procedure QMR01-08-002 Trend Monitoring of Test Results establishes a risk-based trend monitoring program which uses statistical process control and process capability to monitor analytical test results with set action and alert limits for product release attributes, in-process controls, as well as key raw materials, excipients and intermediates. As part of historical trending, action/limit violations are reviewed.

c.

According to CAPA Procedure QCA01-02-001 Potential/Nonconformity Procedure chapter 7.1:

● Corrections are taken to correct the existing nonconformity, where possible.

When a nonconforming product is corrected it shall be subject to reverification to demonstrate conformity to the requirements.

When planning a correction, the following steps are required:

● Document correction plan including:
  - ○ Identity of impacted items to be corrected.
  - ○ Actions that have been or will be taken.
  - ○ Criteria to confirm successful remediation.
  - ○ Who has performed or will perform action(s).
  - ○ Correction due date, with justification.
● Consider if the correction will:
  - ○ impact a regulatory filing
  - ○ adversely impact the item, and/or
  - ○ require validation.

Specific requirements on how to handle material/product (in-process, manufactured or finished) that is nonconforming and requires reprocessing, reworking or re-inspection prior to final release or use in the next processing step are detailed in the procedure QPP01-09-003 Reprocess, Rework, Re-inspections.

In particular, chapter 3.3 and 3.4 provide instructions for rework execution.

Chapter 3.5 provides specific requirements for testing of a reworked batch, while chapter 3.6 provides specific requirements for reevaluation of reworked product:

● Assess the reworked material to ensure it is of a quality equivalent to that normally produced by the process.
● Confirm that all regulatory requirements have been met.
● Ensure that the status is clearly indicated on the product and, if applicable, in the electronic system (SAP).
● Confirm
  - ○ that lots are traceable to their origin
  - ○ an impurity profile assessment has been completed
  - ○ any additional testing in the test plan has been completed and meets expected criteria, and
  - ○ a stability decision has been made and justified.
● Make the final material disposition.

d.

General requirements for creating a CAPA are reported in chapter 7.5 of CAPA procedure QCA01-02-001 Potential/Nonconformity Procedure:

	● Develop a CAPA plan, to address the root/probable cause and contributing factor considering the following: ○ interim action(s) or controls and effectiveness ○ impact to □ regulatory filing □ existing risk document, for example, FMEA □ validation package □ material, process, quality system ○ human error reduction opportunities. Additional instructions on how to develop a CAPA plan are reported in the guideline QCA01-02-001-G003 Potential/Nonconformity Resolution Plan Guideline, chapter 3.5: ● When developing a CAPA plan include: ○ Statement of the cause / contributing factor being addressed by the action. Consider all impacted and related products, processes, systems, etc. that require action to prevent/mitigate recurrence/occurrence. ○ The action(s) needed to prevent/mitigate recurrence/occurrence and how the actions are truly addressing the cause(s) / contributing factor(s). Where a risk assessment exists pertaining to the event, review the existing prevention controls associated with the potential failure cause of the event and identify further controls. Choose the solution that best eliminates or resolves the cause and document the rationale. Consider human error reduction opportunities (training/retraining alone might not be appropriate, specifically if subject event has occurred previously). CAPA which have potential impact on regulatory filings or validation are assessed and controlled through the appropriate quality system. Evidence of completion is provided during the CAPA implementation phase, described in chapter 7.7, in which the following requirements are reported: ● complete actions as outlined in the CAPA plan ● document the actions performed and their outcomes including objective evidence ● route CAPA for approval minimally to Quality. Moreover, the approver has responsibility to review the completed action and outcome against the CAPA plan, as described in chapter 7.8. In addition to the above-mentioned CAPA requirements, QCM01-01 Change Management provides the general requirements for managing changes to methods and procedures. Chapter 2.1 specifies that for changes to product documents, e.g,, testing instructions, packaging or manufacturing processes, the change owner is to use the change management module of the IT system (named SolTRAQs at AbbVie) and any other cross-referenced procedure. The same applies to "product/material specification documents, including test methods, where there is additional impact(s) that must be managed in addition to the document change.". Procedure QCM01-01-001 Proposing a Change defines the steps for completing a change plan in SolTRAQs. The reason for change field should provide a reason for change that links the change to the triggering event, for example CAPA implementation. If the change plan was initiated to address a CAPA, the ER record number is cross-referenced for the effectiveness check. Chapter 5.5 describes that in the referenced records field, reference to related SolTRAQs records (e.g., CAPA, complaints, change plans) should be provided.
e.	Per CAPA policy QCA01 Corrective Action and Preventive Action Policy, the corrective action and preventive action system includes a process for assessing and documenting the impact of an exception, determining when a cause investigation

	is required and communicating exceptions as necessary, and commensurate to the level of risk: ● to management ● to those directly responsible for ensuring the quality of potentially impacted product, process, quality system or study, and ● to external organizations/parties. Personnel responsible for assuring the quality of product or the prevention of problems is directly involved in the CAPA process in the following steps: ● Identifying and initiating an exception report, see chapter 3.0 of CAPA procedure QCA01-02-001 Potential/Nonconformity Procedure: ○ Exception originator is the person who has recognized the non-conformity during the related manufacturing activities, quality verification steps. Exception originator has the following responsibilities: ● Identifies the exception type. ● Initiates the ER. ● Provide the event owner with information for initial impact assessment in case of global ERs. ● During the investigation process ● During CAPA definition ● During CAPA implementation (e.g., procedure/method updates follow the documentation and training flow, for which involved personnel are trained on the new/modified requirements in reference to the event) ● Manager of the area involved by the event has to approve medium and high impact events minimally, see chapter 10.1 of CAPA procedure QCA01-02-001 Potential/Nonconformity Procedure. ● Chapter 14.0 of QCA01-02-001 Potential/Nonconformity Procedure describes how to handle global ERs, which are those that involve more than one site/area/affiliate. Among the other requirements, identifying site/area/affiliate has to: ○ Notify all impacted sites/areas/affiliates and the event owning site of the exception, in addition to the CAPA IT system notification. ● Overall, communicating to management with executive responsibility is assured by QMR01-04-001 Management Review requiring management reviews with required agenda items that include review of significant quality, product and process events and review of quality metrics including key performance indicators, quality trends and/or excursions.
Reviewer Comments	Response is adequate to support the Process Validation and the CAPA Review for the new presentations of the combination product
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

	Date Sent: **3/3/2021**	**Date/Sequence Received:** **3/8/2021**
Information Request #2	**Control Strategy** **NSP-PFS** You provided device verification testing which included Ejection and Activation Force testing of your final finished Pre-filled Syringe with Needle Stick Prevention	

	(NSP-PFS) to verify your Essential Performance Requirement (EPR) of maximum force on the plunger rod for ejection and actuation is not more than (b) (4) under use conditions; however, your provided control strategy does not require this EPR testing after the assembly process. Release testing of your Essential Performance Requirements after the final assembly stage, in addition to the control of incoming components, is necessary to ensure that the final finished combination product reliably and continually meets the acceptable performance limits for its design inputs. Therefore, please implement release controls for your EPR's including ejection and actuation force on the final finished NSP-PFS. **AI** Under S-010, you provided verification testing under use conditions of your final finished Auto-Injector (AI) which included Button Activation Force testing to verify your Essential Performance Requirement (EPR) of force for actuation is between (b) (4) (N) and Needle Shield Retraction Force testing to verify your EPR of the activation feature that must be operated prior to actuation by pushing the combination product against the injection site with a force between (b) (4) N; however, your provided control strategy does not require this EPR testing after the assembly process. Release testing of your Essential Performance Requirements after the final assembly stage, in addition to the control of incoming components, is necessary to ensure that the final finished combination product reliably and continually meets the acceptable performance limits for its design inputs. Therefore, please implement release controls for your EPR's including Button Actuation Force testing and Needle Shield Retraction testing on the final finished AI
Sponsor Response	**NSP-PFS** AbbVie (b) (4) To support implementation of this revision to the control strategy, the documents listed in Table 1 are provided with this response to update the Module 3 CTD sections of BLA 761105/S-009 for the 150 mg/1.0 mL drug product. **AI** AbbVie will (b) (4) implementation of this revision to the control strategy, the documents listed in Table 2 are provided with this response to update the Module 3 CTD sections of BLA 761105/S-010 for the 150 mg/1.0 mL drug product.
Reviewer Comments	Response is adequate to support the control strategy for the new presentations of the combination product
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

<<END OF REVIEW>>

13.APPENDIX A (INFORMATION REQUESTS)

13.1. Interactive Information Requests

13.1.1. Interactive Information Requests sent on Click or tap to enter a date.

3/23/21 IR#3 Response from sponsor
3/19/21 IR#3

- request to reanalyze data or perform additional testing to support 99% reliability related to needle stick prevention attributes of NSP-PFS and AI including "activation at end of injection stroke" and "Maximum force on plunger rod" for the NSP-PFS and "AI Needle shield protection under compression" for the AI.
- Request to add product requirements related to the end of activation cues (visual and audible) for the AI. See above IR in design verification section

3/8/21 IR#2 Response from sponsor
3/3/21 IR#2 request for control plan to incorporate release testing of EPR's for both NSP-PFS and AI (see details above in IR tables)

2/18/21 IR#1 Responsse from sponsor
2/8/21 requests for CAPA information, Process Validation, Risk Analysis, Design Verification (see details above in IR tables)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761105Orig1s009/010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MEMORANDUM

REVIEW OF REVISED 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:	April 13, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761105/S-009
Product Name and Strength:	Skyrizi (risankizumab-rzaa) injection, 150 mg/mL
Applicant/Sponsor Name:	AbbVie, Inc.
OSE RCM #:	2020-1366-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised Instructions for Use (IFU) received on March 22, 2021 and carton labeling and cardboard sleeve labeling received on March 19, 2021 for Skyrizi. The Division of Dermatology and Dentistry (DDD) requested that we review the revised Instructions for Use (IFU), carton labeling, and cardboard sleeve labeling for Skyrizi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

Upon initial review of the revised IFU submitted on March 22, 2021, we determined an additional revision was needed. Specifically, we provided a recommendation via email communication regarding the images in the IFU not accurately representing the cardboard sleeve revision to include blue color. We recommended the figures in the IFU depicting the cardboard sleeve (IFU Step 1 and Step 2) be revised to reflect the blue color on the revised cardboard sleeve." In response, the Applicant submitted a revised IFU on April 7, 2021.

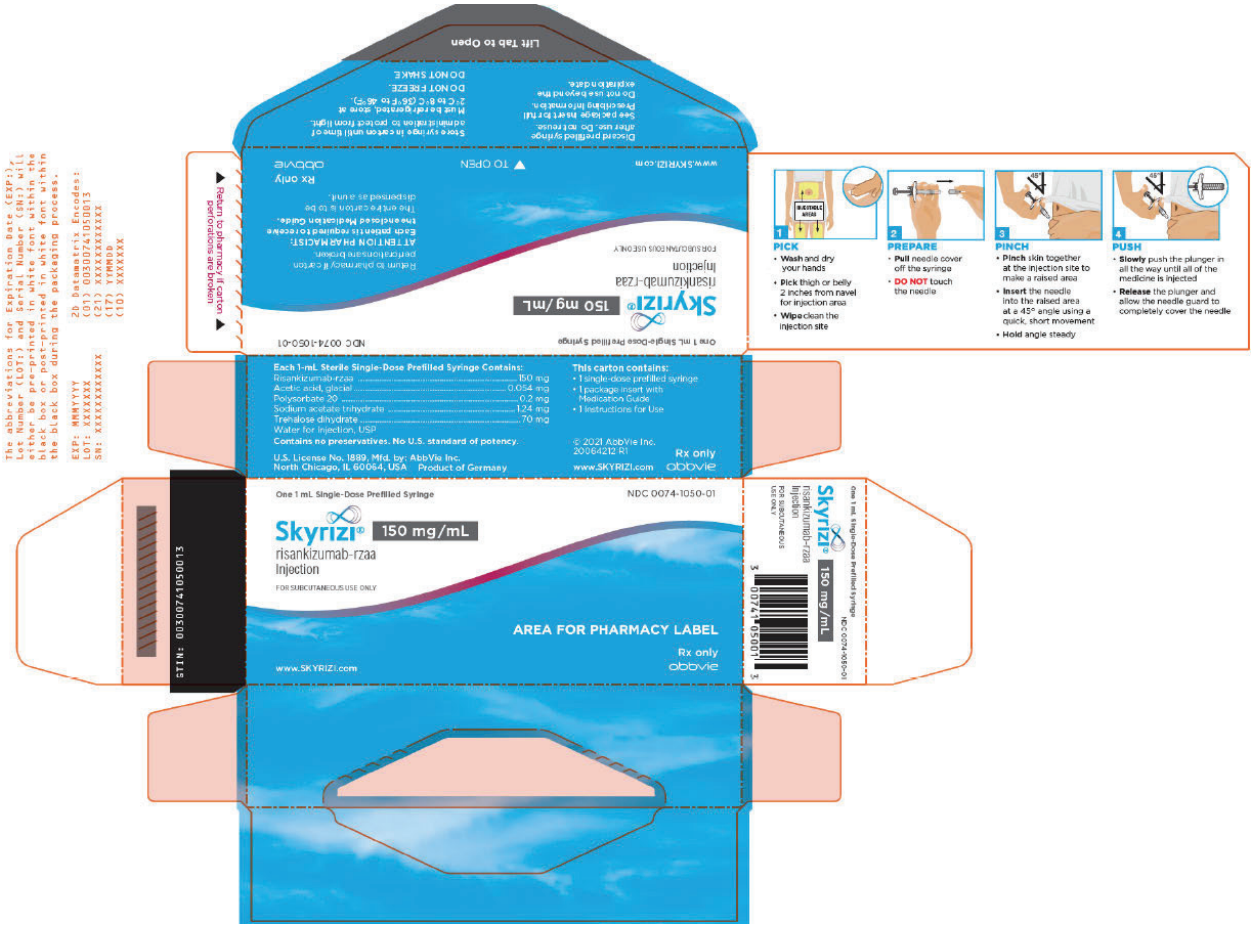
2 CONCLUSION

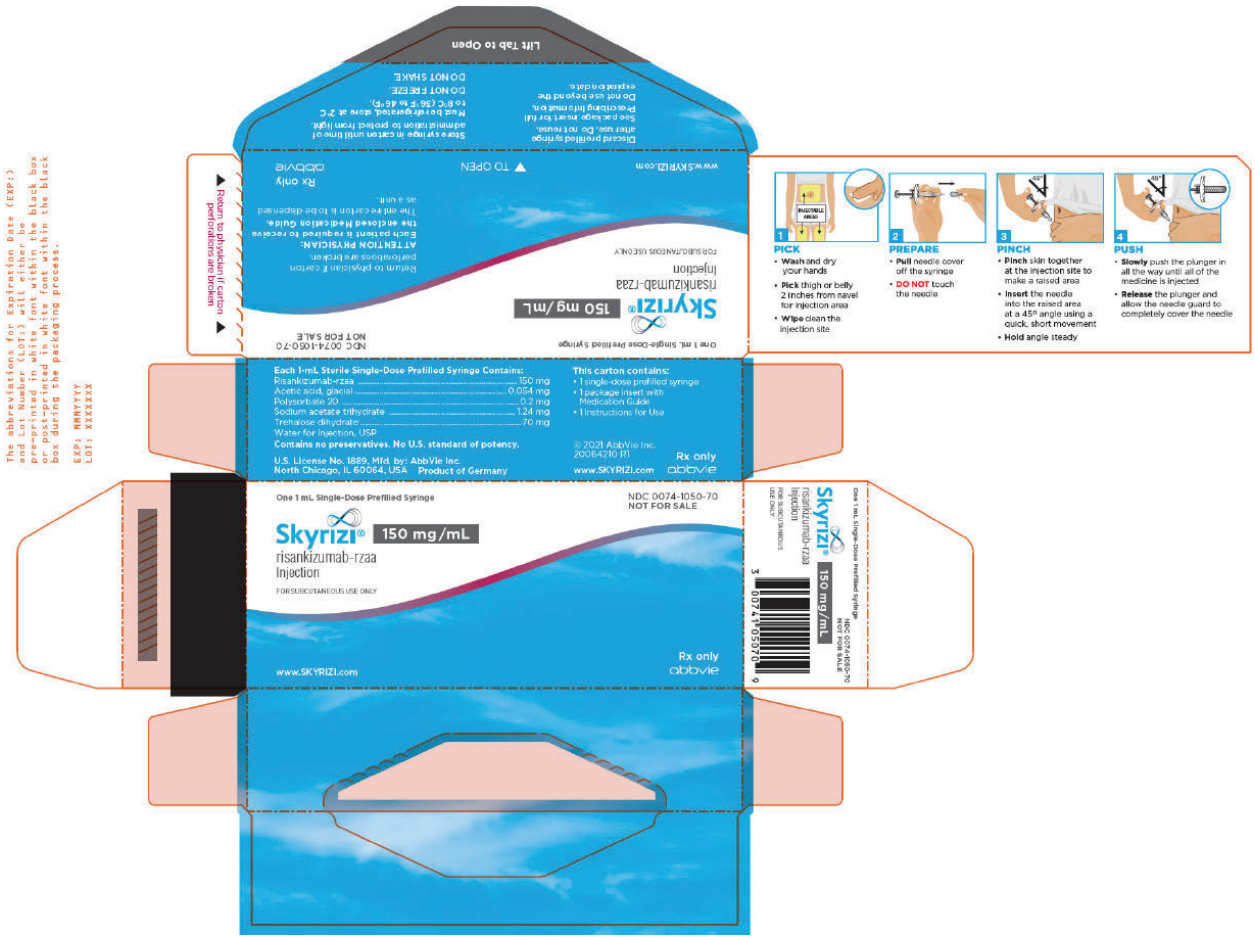
[a] Patel, M. Human Factors Results and Labels and Labeling Review for Skyrizi (BLA 761105/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 15. RCM No.: 2020-1366.

We find the carton labeling, cardboard sleeve labeling, and IFU are acceptable from a medication error perspective.

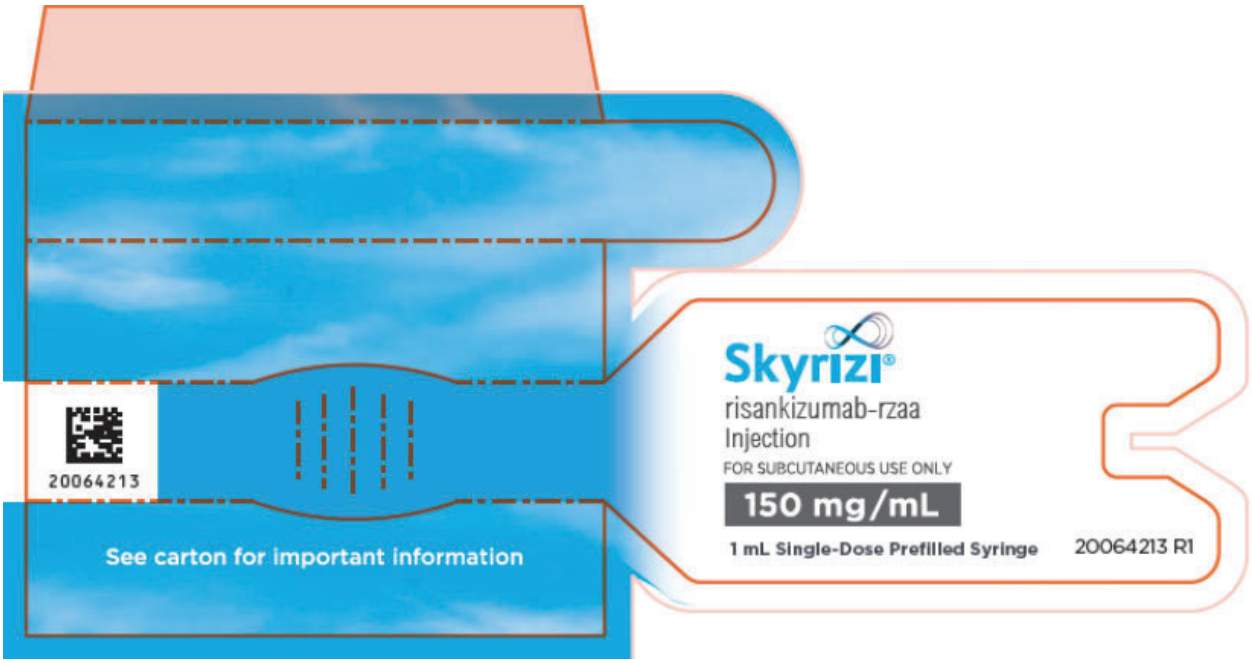
APPENDIX A. IMAGES OF LABELING RECEIVED ON MARCH 19, 2021 AND APRIL 7, 2021

Carton labeling received on March 19, 2021





Cardboard sleeve labeling received on March 19, 2021



Instructions for Use (Image not shown) received on March 22, 2021, available from:

\\CDSESUB1\evsprod\bla761105\0111\m1\us\114-labeling\draft\labeling\draft-cntnr-skyrizi-150mg-1ml-pfs-ifu-20064208-r1.pdf

Instructions for Use (Image not shown) received on April 7, 2021, available from:

\\CDSESUB1\evsprod\bla761105\0118\m1\us\114-labeling\draft\labeling\neg-lbl-6828.pdf

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/s/

MADHURI R PATEL
04/13/2021 03:15:56 PM

EBONY A WHALEY
04/13/2021 03:55:40 PM

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Application #(s):	BLA 761105/S-009 and S-010 SDN 419 and 440
Communication Type:	Correspondence
Communication Group:	Information Request/Advice
Communication Name:	Information Request
Communication ID:	(COR-NDAIR-01)(COR-SNDAIR-01)(COR-BLAIR-01)(COR-SBLAIR-01)
Drafted by:	CJohnson March 18, 2021
Clearance history:	BGould 18 Mar 2021 AWoitach 19 March 2021
Finalized:	CJohnson March 19, 2021
Filename:	
Signatory Authority:	CDTL, Chem TL, Division Director or Deputy. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	Use to obtain clarifying information to assist in completing a review.
Notes:	BLA CMC Supplement Information Request – OBP RPM signs the letter NDA CMC Supplement Information Request – OPQ RPM signs the letter **FOR BLAs:** Use the applicant product code name to identify the proposed biological product because the proper (nonproprietary) name of the biological product is NOT determined until approval. If there is no product code name, contact the Office of Therapeutic Biologics and Biosimilars (OTBB).

Version: 08/27/2020

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

BLA 761105/S-009 and S-010

INFORMATION REQUEST

AbbVie Inc.
Attention: Mary Konkowski
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72 Bldg. AP30-4
North Chicago, IL 60064

Dear Ms. Konkowski:

Please refer to your supplemental biologics license applications (sBLA) dated and received June 26 and July 27, 2020 respectively, submitted under section 351(a) of the Public Health Service Act for Skyrizi (risankizumab-rzaa) injection.

We are reviewing your submissions and have the following comments and information requests. We request a prompt written response by March 22, 2021 in order to continue our evaluation of your supplemental BLA.

1. For both presentations of your combination drug product, the Needle-Stick-Prevention Pre-Filled Syringe (NSP-PFS) and the AutoInjector (AI), you provided verification testing of your needle stick prevention attributes. However, the testing results were based on samples sizes which reflect only a 95% to 97.5% reliability reflecting on risk severity levels of "low" as determined from your risk analyses documentation. We recommend that reliability of 99% as a baseline for any attribute testing related to needle stick prevention based on the identified risk of "infection" from an unintentional needle stick per the FDA guidance document *"Guidance for Industry and FDA Staff - Medical Devices with Sharps Injury Prevention Features"* (https://www.fda.gov/files/medical%20devices/published/Medical-Devices-with-Sharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff-%28PDF%29.pdf). Therefore, reanalyze your data or perform additional testing as necessary to support 99% reliability related to your needle stick prevention attributes of both presentations of your combination product including "activation at end of injection stroke" and "Maximum force on plunger rod" for the NSP-PFS and "AI Needle shield protection under compression" for the AI.

2. You detail verification testing of your AutoInjector including "Actuation" which uses a visual check for the start of actuation and audible checks at the start and end of delivery. However, there is no detail provided for the verification testing

data or acceptance criteria related to this audible feedback (click, timing, correlation with dose delivery) function of your device. Your intended user may solely rely on the audible feedback to indicate end of injection. Therefore, if the click is premature, a wet or incomplete injection could occur. In order to determine whether the design of the audible alarm function is controlled by design and effective, design verification on the volume (i.e., decibels) and timing of the click is necessary. Provide verifiable design input requirements for your audible click timing (+/- seconds from end of injection), volume (i.e., decibels) and residual volume after click (delivered volume remaining in device after audible click).

If you have any questions, please contact Craig Johnson, Regulatory Project Manager, at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Amy Woitach, DO, MS
Clinical Team Leader
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

AMY S WOITACH
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Drafted by:	CJohnson March 4, 2021
Clearance history:	BGould March 4, 2021 AWoitach March 4, 2021
Finalized:	Cjohnson March 10, 2021
Filename:	
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BLA 761105/S-009 and S-010

INFORMATION REQUEST

AbbVie Inc.
Attention: Mary Konkowski
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72 Bldg. AP30-4
North Chicago, IL 60064

Dear Ms. Konkowski:

Please refer to your supplemental biologics license applications (sBLA) dated and received June 26 and July 27, 2020 respectively, submitted under section 351(a) of the Public Health Service Act for Skyrizi (risankizumab-rzaa) injection.

Reference is made to the March 3, 2021 Information Request (IR) for supplements 009 and 010, we are providing a corrected IR for the information requested. We request a prompt written response by March 5, 2021 to this corrected IR in order to continue our evaluation of your supplemental BLA.

1. Under S-009, you provided device verification testing which included Ejection and Activation Force testing of your final finished Pre-filled Syringe with Needle Stick Prevention (NSP-PFS) to verify your Essential Performance Requirement (EPR) of maximum force on the plunger rod for ejection and actuation is not more than (b) (4) (N) under use conditions; however, your provided control strategy does not require this EPR testing after the assembly process. Release testing of your Essential Performance Requirements after the final assembly stage, in addition to the control of incoming components, is necessary to ensure that the final finished combination product reliably and continually meets the acceptable performance limits for its design inputs. Therefore, please implement release controls for your EPR's including ejection and actuation force on the final finished NSP-PFS.

2. Under S-010, you provided verification testing under use conditions of your final finished Auto-Injector (AI) which included Button Activation Force testing to verify your Essential Performance Requirement (EPR) of force for actuation is between (b) (4) Newtons (N) and Needle Shield Retraction Force testing to verify your EPR of the activation feature that must be operated prior to actuation by pushing the combination product against the injection site with a force between (b) (4) N; however, your provided control strategy does not require this EPR testing after

the assembly process. Release testing of your Essential Performance Requirements after the final assembly stage, in addition to the control of incoming components, is necessary to ensure that the final finished combination product reliably and continually meets the acceptable performance limits for its design inputs. Therefore, please implement release controls for your EPR's including Button Actuation Force testing and Needle Shield Retraction testing on the final finished AI.

If you have any questions, please contact Craig Johnson, Regulatory Project Manager, at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Amy Woitach, DO, MS
Clinical Team Leader
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/

AMY S WOITACH
03/11/2021 09:27:30 AM

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Drafted by:	CJohnson March 1, 2021
Clearance history:	BGould March 2, 2021 DKettl March 3, 2021
Finalized:	CJohnson March 3, 2021
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North Chicago, IL 60064

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We are reviewing your submissions and have the following comments and information requests. We request a prompt written response by March 5, 2021 in order to continue our evaluation of your supplemental BLA.

1. You provided device verification testing which included Ejection and Activation Force testing of your final finished Pre-filled Syringe with Needle Stick Prevention (NSP-PFS) to verify your Essential Performance Requirement (EPR) of maximum force on the plunger rod for ejection and actuation is not more than (b) (4) Newtons (N) under use conditions; however, your provided control strategy does not require this EPR testing after the assembly process. Release testing of your Essential Performance Requirements after the final assembly stage, in addition to the control of incoming components, is necessary to ensure that the final finished combination product reliably and continually meets the acceptable performance limits for its design inputs. Therefore, please implement release controls for your EPR's including ejection and actuation force on the final finished NSP-PFS.

2. You provided device verification testing which included Ejection and Activation Force testing of your final finished Pre-filled Syringe with Needle Stick Prevention (NSP-PFS) to verify your Essential Performance Requirement (EPR) of maximum force on the plunger rod for ejection and actuation is not more than (b) (4) Newtons (N) under use conditions; however, your provided control strategy does not require this EPR testing after the assembly process. Release testing of your Essential Performance Requirements after the final assembly stage, in addition to the control of incoming components, is necessary to ensure that the final

finished combination product reliably and continually meets the acceptable performance limits for its design inputs. Therefore, please implement release controls for your EPR's including ejection and actuation force on the final finished NSP-PFS.

If you have any questions, please contact Craig Johnson, Regulatory Project Manager, at 301-796-3921.

Sincerely,

{See appended electronic signature page}

David Kettl, MD, FAAP
Clinical Team Leader
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

DAVID L KETTL
03/03/2021 03:53:51 PM

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

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

Memorandum

Date: March 2, 2021

To: Amy Woitach, DO, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)

David Kettl, MD, Clinical Team Leader, DDD

Craig Johnson, PharmD, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matt Falter, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for SKYRIZI® (risankizumab-rzaa) injection, for subcutaneous use (Skyrizi)

BLA: 761105/Supplements 009 and 010

In response to DDD's consult request dated August 19, 2020, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the supplemental BLA submissions for Skyrizi. These supplements (S009 and S010) provide for new product formulations and presentations.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DDD on February 25, 2021 and we have no additional comments at this time.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on September 4, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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/s/

LAURIE J BUONACCORSI
03/02/2021 08:15:49 AM

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: February 16, 2021

TO: Kendall Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation

FROM: Kara A. Scheibner, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly Benson, Ph.D.
Deputy Director
(DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Remote Record Review (RRR) of AbbVie Deutschland GmbH and Co KG, Ludwigshafen, Germany

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the analytical portion of Study M15-990 (BLA 761105/S009/S010, Risankizumab) conducted at AbbVie Deutschland GmbH and Co KG (AbbVie).

We observed objectionable findings that may impact the reliability of study data.

1.1. Recommendation

Based on my review of the RRR findings (and the firm's response to the RRR findings), we conclude that data from the audited study may be impacted by Finding 1. However, as clinical implications of Finding 1 on study M15-990 cannot be determined from the RRR, we recommend that the Review Division consider whether there is an impact on clinical data.

2. Reviewed Studies

Study M15-990 (BLA 761105/S009/S010)
"A Phase 1 study in healthy volunteers to evaluate the bioavailability of risankizumab new formulation in pre-filled

syringe relative to 90 mg/mL formulation in pre-filled syringe and characterization of risankizumab pharmacokinetics using new formulation in auto-injector"
Sample Analysis Period: 10/09/2019 to 12/09/2019 (pharmacokinetics, PK) and 10/31/2019 to 12/11/2019 (anti-drug antibodies, ADA)

3. Scope of RRR

OSIS scientist Kara A. Scheibner, Ph.D. reviewed the analytical portion of the above studies conducted at AbbVie Deutschland GmbH and Co KG, Ludwigshafen, Germany from 12/07/2020 to 12/11/2020.

The RRR included an examination of study records (e.g., shipping, reagent preparation, audit trails, sample preparation, etc.), method validation records, and sample analysis records. AbbVie provided a virtual tour of the facility that enabled me to view the automation equipment used for method validation and study sample analysis. I also interviewed AbbVie's management and staff, and reviewed equipment logs, investigation documents, and relevant SOPs.

4. RRR Findings

At the conclusion of the RRR, I observed objectionable findings that may impact reliability of study data. I discussed the following items with the firm's management during the RRR close-out meeting.

My evaluation of the findings that were discussed (and the firm's response dated 12/22/2020 (**Attachment 1**) are presented below.

4.1. Findings discussed at the close-out of RRR

4.1.1. Item 1 - During ADA sample analysis, 470 samples were assessed in the presence of drug concentrat exceeding the validated drug tolerance of the ADA assay (b) (4) ng/mL of risankizumab in serum).

Firm's Response: AbbVie stated that drug tolerance of assay was determined using two ADA positive controls, (b) (4) ng/mL. While the performance of the 6 ng/mL tive c tolerated risankizu concentrations up to (b) (4) ng/mL, the performance of (b) (4) ng/mL positive contro s risankizumab-tolerant up to (ng/mL of the drug. The highest risankizumab co ation detected in study M15-990 was (b) (4)

ng/mL. Thus, they concluded that ADA detection would be possible for study samples containing ADAs in the range of 100 ng/mL, which follows agency recommendations for assay sensitivity to detect clinically meaningful ADA responses.

AbbVie stated that they understand ADA assessment is dependent on the drug tolerance of the ADA assay and the drug concentration present in individual subject samples. As a corrective action, they will include a statement with details for specific drug tolerance levels of the ADA assay in all ADA reports for studies supporting risankizumab.

OSIS Evaluation: OSIS acknowledges AbbVie's response to this finding. We agree that, given the method validation data cited in their response, samples with ADA concentrations in the range of 100 ng/mL would likely be detectable in the assay. The positive control used in drug tolerance assessments was a polyclonal antibody, which was used to closely mimic the likely physiological response to risankizumab exposure.

However, the ECL (electrochemiluminescence) values of 100 ng/mL ADA-positive control samples in the drug tolerance assay (**Table 116** of the method validation report) were >1000 units. Only ten (10) ADA samples in study M15-990 had ECL values >1000 units. The majority of ADA samples yielded ECL values similar to the 6 ng/mL low ADA-positive control. In addition, there is an inverse correlation between drug concentrations and ECL values from the ADA assay (see **Exhibit 1**). OSIS also noted an increase in ECL values when ADA samples with higher risankizumab concentrations that were diluted 30-fold compared to samples that were diluted 10-fold, suggesting potential risankizumab interference (**Exhibit 1**).

These data suggest that high risankizumab serum concentrations may affect the ability to determine ADA-positive samples. Based on the risankizumab serum concentrations in samples from study M15-990, the ability to determine ADA-positive samples may be affected. However, additional information supports the potential that ADA-positive samples in study M15-990 could still be determined. For example, study samples with ECL values below 1000 units (i.e. below the ECL values yielded with the 100 ng/mL ADA-positive control) did confirm positive and yielded substantial titer values. Furthermore, the ADA assay had a sensitivity of 1.21 ng/mL (manual assay execution) and 1.36 ng/mL (automated assay execution), which is well below the routine recommendation of acceptable sensitivity of 100 ng/mL or

less. In addition, the overall study yielded a high false positive rate (~30%).

In conclusion, OSIS finds that drug tolerance of the ADA assay may impact the ability to detect ADA-positive samples in the presence of high risankizumab concentrations in study M15-990. However, given the high sensitivity of the ADA assay and the high false positive rate of study M15-990, the overall outcome of the study is unlikely to be affected. We note that clinical implications on safety and efficacy are beyond the scope of the remote record review. Thus, we recommend that the Review Division consider whether this finding will impact the clinical evaluation of the data, and whether Finding 1 will impact additional risankizumab studies conducted at AbbVie using the same ADA method.

4.1.2. Item 2 - During ADA sample analysis, samples in Run 40 were repeated inadvertently in Run 176. Results from the inadvertent reassay in Run 176 were used to determine the final reported result despite obtaining valid results in Run 40.

Firm's Response: AbbVie stated that the results obtained in Run 176 were obtained inadvertently due to the accidental reanalysis of samples from Run 40. Results from Run 176 were valid and were comparable to the original results obtained in Run 40. Thus, per SOP Q-10-10-022 (versions 8 and 9, **Exhibit 2**), the firm's processes were followed.

AbbVie acknowledged that their repeat analysis processes could be improved by adding specific details to their SOP and committed to making these changes.

OSIS Evaluation: OSIS acknowledges AbbVie's response to this finding, and finds their response acceptable. Given that the inadvertent repeat data fell within AbbVie's acceptance criteria for reanalysis and did not alter the ADA results (e.g. all ADA-positive and ADA-negative samples remained as such), there is no impact to the reliability of data from study M15-990. However, subsequent inspections or RRRs should verify implementation of the proposed changes to ensure the reliability of their repeat analysis processes.

5. Conclusion

After review of the RRR findings, we conclude that data from the audited study may be impacted. Drug tolerance limitations of the

assay cited in Finding 1 may impact the ability of the assay to detect ADA-positive samples in the presence of high risankizumab concentrations. Due to the high sensitivity of the assay, and the high false positive rate of the study, the overall conclusions for study M15-990 are likely unaffected. However, as clinical safety and efficacy implications of Finding 1 cannot be determined from the remote record review, we recommend that the Review Division consider whether this finding will impact the clinical evaluation of the data. We recommend that future RRRs or inspections follow-up on AbbVie's proposed corrective actions.

cc:
OTS/OSIS/Kassim/Folian/Irier/Pham/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Skelly/Au/Scheibner

Draft: KAS 02/05/2021; KAS 02/11/2021
Edit: MFS 02/08/2021; KAB 02/11/2021; KAB 02/16/2021

ECMS:
http://ecmsweb.fda.gov:8080/webtop/component/drl?objectId=0b0026f883ee4e45&Reload=1612535722740

OSIS File #: BE8971 (BLA 761105/S-009) and BE8983 (BLA 761105/S-010)

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/s/

KARA A SCHEIBNER
02/16/2021 03:21:28 PM

MICHAEL F SKELLY
02/16/2021 03:24:31 PM

KIMBERLY A BENSON
02/16/2021 03:39:06 PM

DOCUMENT INFORMATION PAGE

This page is for FDA internal use only. **Do NOT send this page with the letter.**

Application #(s):	BLA 761105/S-009 and S-010 SDN 419 and 440
Communication Type:	Correspondence
Communication Group:	Filing
Communication Name:	No Filing Review Issues Identified
Communication ID:	(COR-NDAFILE-05)(COR-SNDAFILE-05)(COR-BLAFILE-05)(COR-SBLAFILE-05)
Drafted by:	CJohnson September 1, 2020
Clearance History:	BGould 01 Sep 20 DKettl 02 Sep 20 STargum 03 Sept 2020
Finalized:	CJohnson September 3, 2020
Filename:	
PDUFA Goal Impact:	Closes 74 day goal
Signatory Authority:	Division Director. Deputy Director or CDTL who is covering for the Division Director may sign on behalf of the Division Director (i.e., the signature block on the letter will not change). **Signature block should not be changed from Division Director.** However, DD can down delegate and designee can sign as "For DD."
Use Statement:	Use to notify the applicant that no review issues were identified during the initial filing review for an application that is deemed fileable. **Do not use this letter for a 351(k) (biosimilar) application. Use 351(k) "No Filing Review Issues Identified" letter**
Notes:	**Filing review issues, or substantive review issues identified by the review team during the initial filing review, are distinct from deficiencies that serve as the basis for a Refusal to File action. For more information, refer to MAPP 6010.5:** http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/ucm081990.pdf **NOTE**: For a Priority Review, use one of the following 3 options:

(1) If you have filing review issues but they are not ready to send to applicant by Day 60, send the "Priority Review Determination" letter (COR-NDAFILE-06)(COR-SNDAFILE-06)(COR-BLAFILE-06)(COR-sBLAFILE-06) by Day 60 then send the "Filing Review Issues Identified" Letter (COR-NDAFILE-04) (COR-SNDAFILE-04)) (COR-BLAFILE-04)(COR-SBLAFILE-04) by Day 74.
(2) If you have filing review issues and they are ready to send to the applicant by Day 60, send the "Filing Review Issues Identified" Letter (COR-NDAFILE-04) (COR-SNDAFILE-04)) (COR-SNDAFILE-04) (COR-BLAFILE-04) (COR-SBLAFILE-04) by Day 60.
(3) If you have no filing review issues, send the "No Filing Review Issues Identified" Letter (COR-NDAFILE-05) (COR-sNDAFILE-05) (COR-BLAFILE-05)(COR-sBLAFILE-05)) to the applicant by Day 60.

For a Standard Review, send either the "Filing Review Issues Identified" Letter (COR-NDAFILE-04)(COR-sNDA-04)(COR-BLA04)(COR-sBLA04) or the "No Filing Review Issues Identified" Letter (COR-NDAFILE-05) (COR-sNDAFILE-05) (COR-BLAFILE-05)(COR-sBLAFILE to the applicant by Day 74.

If the application is on AIP, consult the CDER AIP Coordinator (Jagjit Grewal) regarding the title and content of this letter.

FOR BLAs: Use the applicant product code name to identify the proposed biological product because the proper (nonproprietary) name of the biological product is NOT determined until approval. If there is no product code name, contact the Office of Therapeutic Biologics and Biosimilars (OTBB).

Version: 02/18/2020

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

BLA 761105/S-009 & S-010

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

AbbVie Inc.
Attention: Mary Konkowski
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA72 Bldg. AP30-4
North Chicago, IL 60064

Dear Ms. Konkowski:

Please refer to your supplemental biologics license applications (sBLA) S-009 and S-010, submitted under section 351(a) of the Public Health Service Act for Skyrizi (risankizumab-rzaa) injection dated and received June 26 and July 27, 2020 respectively.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 26, 2021.

We are reviewing your application according to the processes described in the draft guidance for industry *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*.[1] Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 17, 2021. This date conforms to the 21st Century Review timeline for your application.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and PLLR Requirements for Prescribing Information[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU).

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[2] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[4]

Do not submit launch materials until you have received our proposed revisions to the Prescribing Information (PI), Medication Guide, and Instructions for Use (IFU), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see FDA.gov.[5] If you have any questions, call OPDP at 301-796-1200.

If you have any questions, call Craig Johnson, Regulatory Project Manager, at 301-796-3921.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

[4] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[5] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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/s/

SHARI L TARGUM
09/03/2020 02:11:03 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Instructions | Submission Information

Date	8/27/2020		
To:	ANH-THY LY		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	N/A-OPQ/OSE led
From	Rob Nakielny OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Director OPEQ/OHT3/DHT3C		
Subject	BLA 761105 , SKYRIZI (risankizumab-rzaa) ICC2000658, 2000659, 2000676 Case #00025444, 00025445, 00025806		
Recommendation	**Filing Recommendation Date: 8/25/2020** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. see Section 5.4 Filing Review Conclusions ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: Click or tap to enter a date. ☐ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)

Remove Buttons

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761105 Supplement 74 and 79
Sponsor	AbbVie Inc.
Drug/Biologic	SKYRIZI (risankizumab-rzaa)
Indications for Use	Treatment of moderate-to-severe plaque psoriasis in adults who are candidates fo rsystemic therapy or phototherapy
Device Constituent	Pre-Filled Syringe, Autoinjector
Related Files	None

Review Team		
Lead Device Reviewer	*Rob Nakielny*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	
Interim Due Dates	**Meeting/Due Date**
Filing	08/25/20, 09/25/20
74-Day Letter	
Mid-Cycle	
Primary Review	12/11/20, 03/01/21
Internal Meeting(s)	
Sponsor Meeting(s)	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description				
Labeling				
Design Controls				
Risk Analysis				
Design Verification				
Consultant Discipline Reviews				
Clinical Validation				
Human Factors Validation				
Facilities & Quality Systems				

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☐

TABLE OF CONTENTS

Update Table of Contents

3. PURPOSE/BACKGROUND

3.1. Scope

AbbVie Inc. is requesting approval of SKYRIZI (risankizumab-rzaa). The device constituent of the combination product is a Pre-Filled Syringe per supplement #9 and an Auto-Injector per supplement #10 .

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Review of the submitted AI and PFS to support approval of the new route of administration.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device performance, Biocompatibility (non-drug contacting), inspection status (of AI device only).

This review will not cover the following review areas:

Drug product quality, human factors

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
SKYRIZI (risankizumab-rzaa)	Treatment of moderate-to-severe plaque psoriasis in adults who are candidates fo rsystemic therapy or phototherapy
Pre-Filled Syringe & Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
74	3.2.P.7 Container Closure System
79	3.2.P.7 Container Closure System
79	3.2.P.3.1 Manufacturer(s)
79	3.2.P.2 Pharmaceutical Development

4. DEVICE DESCRIPTION

4.1. Device Descriptions

The following information was obtained from:

- Sequence 74, PFS+NSP
- Sequence 79, AI

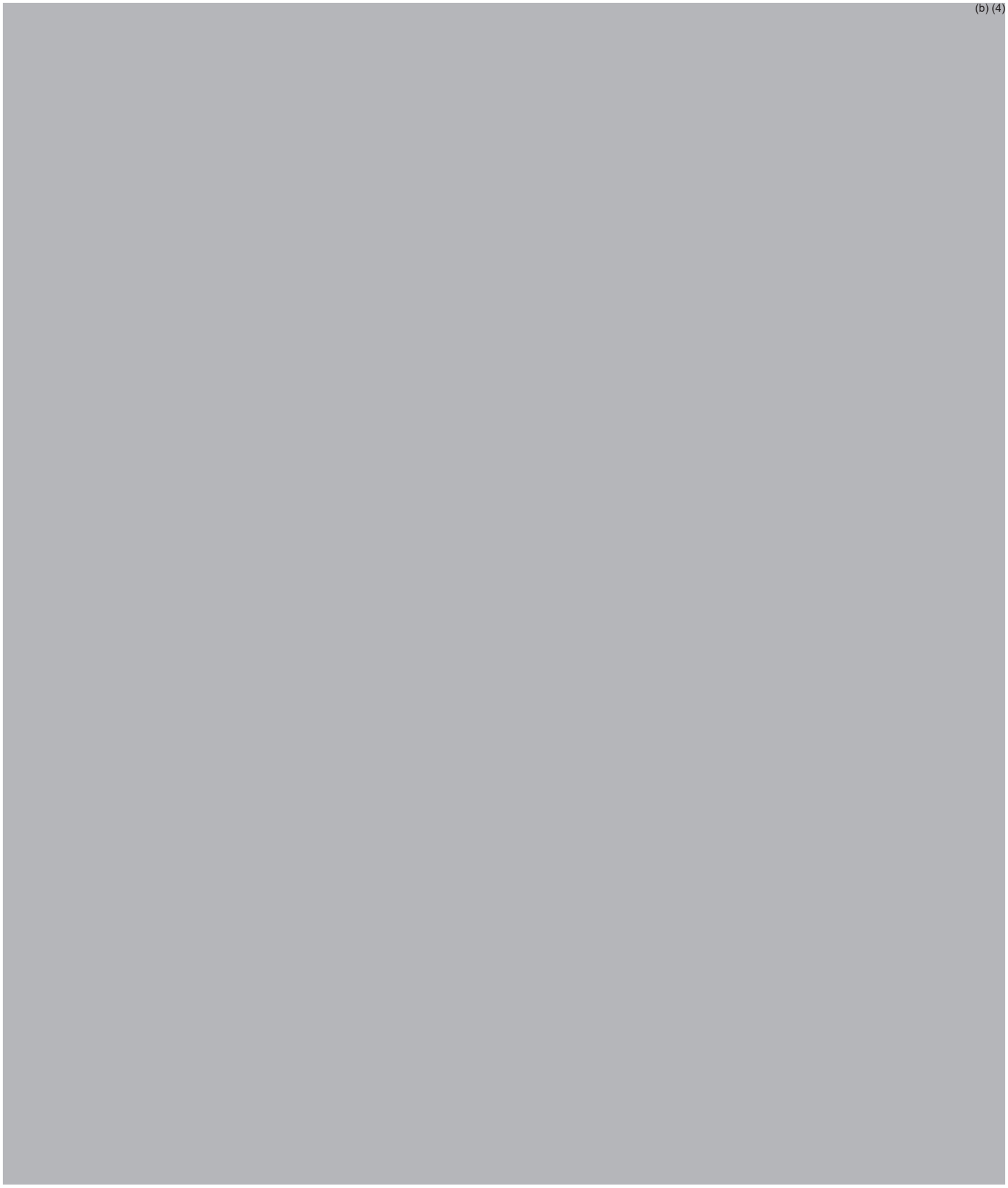
Sequence 74 PFS+NSP

The Pre-filled Syringe + Needle Stick Prevention is for subcutaneous administration of Risankizumab 150 mg/mL. The components which make up the device are identified in table 1.

Table 1. Component description for PFS+NSP

(b) (4)

(b) (4)



(b) (4)

4.2. Steps for Using the Device

PFS: Remove cap, insert needle, depress plunger
AI:

1. Remove RNS (Rigid needle shield) remover cover from the AI.
2. Press against skin
3. Press the trigger button of the AI for delivery of the drug product solution
4. End of delivery, inspection window is yellow and audible click is presented.
5. Remove from skin

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		

The Device description is adequate.
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility	X		
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation	X		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment
The sponsor provided sufficient information to begin review.

5.2. Facilities Information

Firm Name:	Abbvie Deutschland Gmbh & Co. KG
Address:	Knollstrasse 67061 Ludwigshafen Germany
FEI:	3002807401
Responsibilities:	Final Assembly of the Auto-Injector drug product

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 6/19/2017 to 6/23/2017. The inspection covered both drug CGMPs and medical device QS and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A post-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, a recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

Add Additional Facility

Reviewer Comment
Scope of the review of the assembly facilities is limited to the AI device only.
The proposed Post Approval Inspection is based on the fact that the last inspection of the manufacturing facility was performed 3 years ago; however, the manufacturing facility inspection at that time resulted in NAI, the facility is experienced in manufacturing medical devices, and the device is a non emergency use product.

5.3. Filing Review Conclusion

FILING REVIEW CONCLUSION

Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A

Facilities Inspection Recommendation:
☐ (PAI) Pre-Approval Inspection ☑ Post-Approval Inspection ☐ Routine Surveillance
☐ No Inspection ☐ N/A

Site(s) needing inspection: Abbvie Deutschland Gmbh & Co. KG

Reviewer Comments

We are recommending Post-Approval Inspection for the AI manufacturing facility.
Refuse to File Deficiencies: ☐ Yes ☐ No ☑ N/A
74-Day Letter Deficiencies: ☐ Yes ☐ No ☐ N/A

Add Additional Information Request

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.			
Drug name is visible on device constituent and packaging			
Device/Combination Product Name and labeling is consistent with the type of device constituent			
Prescriptive Statement/Symbol on device constituent			
Warnings			
Contraindications			
Instructions for Use			
Final Instructions for Use Validated through Human Factors			
Electrical Safety Labeling/Symbols			
EMC Labeling/Symbols			
Software Version Labeling			
MRI Labeling/Symbols			
RF/Wireless Labeling/Symbols			

Reviewer Comments

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A

Reviewer Comments

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by ☐ Insert Consultant Name ; The full memo is located in Appendix B. ☐ The Lead Reviewer Below is a summary of the review & recommendation:

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Labeling Review Section**

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product			
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)			

Mitigations are adequate to reduce risk to health			
Version history demonstrates risk management throughout design / development activities			
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)			
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing			
To-be-marketed device was used in the pivotal clinical trial			
Bioequivalence Study utilized to-be-marketed device			
Verification methods relevant to specific use conditions as described in design documents and labeling			
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			
Traceability demonstrated for specifications to performance data			

Reviewer Comments

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)

Reviewer Comments

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	
IEC 60601-1-2:2014	
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	

Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	
Applying Human Factors and Usability Engineering to Medical Devices	

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

Follow-On Deficiency	Date Sent: Click or tap to enter a date.	Date/Sequence Received: Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Design Control Review Section**

8. RISK ANALYSIS

8.1. Risk Management Plan

Reviewer Comments

8.2. Hazard Analysis and Risk Summary Report

Link to Infusion Pump SAC Reviewer Guide

Reviewer Comments

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Risk Analysis Review Section**

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)

Reviewer Comment

9.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)

Reviewer Comment

9.1.3. Evaluation of Test Methods

Title:	
Scope/Objective & Acceptance Criteria:	
Methods	
Results:	
Conclusions/ Reviewer Comments:	
Acceptable:	☐Yes ☐No

Reviewer Comment

Insert Additional Design Verification Table

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Design Verification Review Section**

9.3. Discipline Specific Sub-Consulted Review Summary

☐ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

Discipline-Specific Design Verification / Validation adequately addressed						
Discipline	**Consult needed**			**Consultant**	**Section**	**Adequately Addressed (Y/N/NA)**
	Yes	**No**	**N/A**			
Engineering (Materials, Mechanical, General)						
Biocompatibility						
Sterility						
Software / Cybersecurity						
Electrical Safety / EMC						
Human Factors					11	
Clinical						

CDRH sent Deficiencies or Interactive Review Questions to the Sponsor	☐ **Yes** ☐ **No**

Discipline: **Consultant:**	**Date Sent:** Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency Discipline: **Consultant:**	**Date Sent:**	**Date/Sequence Received:**
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Consultant Deficiency Review Section**

9.3.1. Insert Discipline Review

The following Insert Discipline review was completed by Insert Consultant Name. The full memo is located in **Appendix B**. Below is a summary of the recommendation:

Insert Discipline Review Section

☐ **No Additional Disciplines**

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review
☐ There are clinical studies for review
This information was obtained from the following **documents**:

Study Name	
Study Type	
Objectives/Endpoints	
Drug/Device Studied	
Number and Type of Subjects	

Brief description of protocol	
Results	
Device Related Comments	
Reviewer Comments	
Reviewer Conclusion	

Reviewer Comment

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Clinical Validation Review Section**

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted		☐
Human Factors deferred to DMEPA	Review Instructions	☐

CDRH Human Factors Review incorporates comments and considerations by the multi-disciplinary review team.

- Lead Reviewer – Rob Nakielny
- Human Factors Consultant – Name, full memo located in Appendix B
- Clinical Consultant – Name or N/A, full memo located in Appendix B

Documents Reviewed

Human Factors Documentation Supporting the Combination Product

Study Protocol/Report	Study Title

11.1. Review Summary and Recommendations

CDRH finds the Human Factors/Usability Report (Data):

- ☐ Acceptable and have no additional recommendations.
- ☐ Not Acceptable. We have additional comments to convey, **see Sections 11.1.2 and 11.1.3.**

There are other sections within the lead review memo which may impact the review of the Human Factors Validation. Please see the box below describing these issues:

11.1.1. High-Level Reviewer Conclusions

Lead Reviewer Conclusions

Below is a summary of the recommendation:

Human Factors Consultant Conclusions

The following Human Factors Consulting review was completed by HF Consultant Name. The full memo is located in Appendix B. Below is a summary of the recommendation:

Clinical Consultant Conclusions

☐ No Clinical Consult was Issued

The following Clinical Consulting review was completed by Clinical Consultant Name. The full memo is located in Appendix B. Below is a summary of the recommendation:			
Yes	No	NA	
			The type of participants in the human factors study are appropriate
			The environment in the human factors study is appropriate
			The protocol mirrors clinical practice
			The critical tasks are clinically representative
Additional Comments			

11.1.2. Comments to DMEPA

11.1.3. 'Letter-Ready' Deficiencies

☐ CDRH has no Human Factors related Major Deficiencies

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

☐ HFPMET Concurrence with Major Deficiencies below

Major Deficiencies

11.2. Combination Product Background Information

	Summative Study	Marketed/Intended
Environment of use/ Conditions of use		
Test Participants/Users		
Description of Device used and how it compares to the to be marketed device		
Training		

Reviewer Comments

11.3. Human Factors Report Review

The following review is based on content described in "Applying Human Factors and Usability Engineering to Medical Devices Guidance for Industry and Food and Drug Administration Staff," issued February 3, 2016. Sponsors are not required to submit in the prescribed format of the guidance document, however, the report should contain all the same elements as described in the table below. Per this guidance, CDRH defines a critical task as the following: *"A user task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care."*

Report Contents		Present (Y/N/NA)	Adequate (Y/N/NA)
Human Factors Report Context	Intended use and operational contexts of use		
	Intended user population(s) and meaningful differences in capabilities between multiple user populations that could affect user interactions with the device		
	Number and type of test participants		
	Use environments and conditions that could affect user interactions with the device		
	Test environment and conditions of use		
	Graphical representation of device and its user interface		
	Description of device user interface		
	Device labeling		
	Overview of operational sequence of device and expected user interactions with user interface		

Reviewer Comments			
Report Contents		**Present (Y/N/NA)**	**Adequate (Y/N/NA)**
Training	Training provided to test participants and how it corresponded to real-world training levels		
Reviewer Comments			

Report Contents		**Present (Y/N/NA)**	**Adequate (Y/N/NA)**
Summary of known use problems and formative human factors/usability studies	Known use problems with previous models of the subject device		
	Known use problems with similar devices, predicate devices or devices with similar user interface elements		
	Key results of formative human factors/usability studies		
	Key findings that informed the human factors summative test protocol		
Reviewer Comments			

Report Contents		**Present (Y/N/NA)**	**Adequate (Y/N/NA)**
Description and categorization of critical tasks	Process used to identify critical tasks		
	List and descriptions of critical tasks		
	Categorization of critical tasks by severity of potential harm		
	Descriptions of use scenarios that include critical tasks		
	Critical Tasks list is adequate		
Reviewer Comments			

Report Contents		**Present (Y/N/NA)**	**Adequate (Y/N/NA)**
Analysis of hazards and risks associated with use of the device	Potential use errors		
	Potential harm and severity of harm that could result from each use error		
	Risk management measures implemented to eliminate or reduce the risk		
	Description and categorization of critical tasks		
Reviewer Comments			

Report Contents		**Present (Y/N/NA)**	**Adequate (Y/N/NA)**
Human Factors Protocol Details	Rationale for test type selected (i.e., simulated use, actual use or clinical study)		
	Critical tasks and use scenarios included in testing		
	Definition of successful performance of each test task		
	Description of data collection plans for objective and subjective data.		
	Description of plan for data analysis and closure of the Human Factors Validation activities.		
Reviewer Comments			

Report Contents		**Present (Y/N/NA)**	**Adequate (Y/N/NA)**
Human Factors Result Details	Test results: Observations of task performance and occurrences of use errors, close calls, and use problems		

	Test results: Feedback from interviews with test participants regarding device use, critical tasks, use errors, and problems (as applicable)		
	Description and analysis of all use errors and difficulties that could cause harm, root causes of the problems, and implications for additional risk elimination or reduction		
	Statement that the device has been found to be safe and effective for the intended users, uses, and use environments		
	Brief summary of HFE/UE processes and results that support this conclusion		
	Discussion of residual use-related risk		
Reviewer Comments			

11.3.1. Discussion of Results and Use Errors

Analysis Table Compiled from HF Validation Results

Use Errors/Close Calls/Difficulties	Where Captured/Subtask	Root Cause Analysis	Potential hazard or harm	Further risk control necessary?

11.3.2. Device Modifications after Summative Study

Reviewer Comments

11.4. Human Factors Review Conclusion

HUMAN FACTORS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Human Factors Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Human Factors Validation Review Section**

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☐

Facility Regulatory History Review	
Firm Name:	
Address & FEI:	
Responsibilities:	
Site Inspection Recommendation:	Choose an item.

Reviewer Comments

Add Facility

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☐ Yes	☐ No

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

The Sponsor provided the following production/manufacturing flow diagram that identifies the steps involved in the manufacture of the finished combination product. The diagram includes all steps involved in the manufacturing and assembly of the device constituent parts of the combination product:

Reviewer Comments

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☐Yes	☐No

12.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

What Quality System did the Sponsor choose:

☐ Device QSR-based

☐ Drug cGMP-Based Streamline – Review Instructions

☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s):	**Reviewer Discussion** –
21 CFR 820.30 Summary of Design Controls	Firm(s):	**Reviewer Discussion** – Reviewed in detail in Section 7
21 CFR 820.50 Summary of Purchasing Controls	Firm(s):	**Reviewer Discussion** –
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s):	**Reviewer Discussion** – Reviewed in Section 12.2.3.
21 CFR 820.170 Summary of Installation	Firm(s):	**Reviewer Discussion** –
21 CFR 820.200 Summary Servicing	Firm(s):	**Reviewer Discussion** –
Subpart F – Identification and Traceability	Firm(s):	**Reviewer Discussion** –
Subpart G – Production and Process Controls	Firm(s):	**Reviewer Discussion** – Reviewed in Section 12.3
Subpart H – Acceptance Activities	Firm(s):	**Reviewer Discussion** –

Subpart I – Nonconforming Product	Firm(s):	**Reviewer Discussion** –
Subpart K – Labeling and Packaging Controls	Firm(s):	**Reviewer Discussion** –
Subpart L – Handling, Storage, Distribution	Firm(s):	**Reviewer Discussion** –
Subpart M – Records	Firm(s):	**Reviewer Discussion** –
Subpart O – Statistical Techniques	Firm(s):	**Reviewer Discussion** –

Reviewer Comments

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☐ Yes	☐ No

12.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

The following table reflects whether the Sponsor addressed the required elements of corrective and preventive action controls:

CAPA Procedure Required Elements	Present
Procedures include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems.	
Procedures include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use.	
Procedures include appropriate statistical analysis of these quality data to detect recurring quality problems	
Investigations into the cause of nonconformities relating to product, processes, and the quality system	
Includes requirements for identification and implementation of actions needed to correct and prevent recurrence of nonconformities and other quality problems	
Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device	
Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications	

Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems	
Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems	
Submits relevant information on identified quality problems, as well as corrective and preventive actions, for management review	
Requires documentation of all CAPA activities	

Reviewer Comments

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☐Yes	☐No

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
EPR #1		
EPR #2		
EPR …		

Reviewer Comments

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☐Yes	☐No

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Follow-On Deficiency	**Date Sent:** Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Facilities & QS Review Section**

<<END OF REVIEW>>

13.APPENDIX A (INFORMATION REQUESTS)

13.1. Filing/74-Day Information Requests

13.2. Mid-Cycle Information Requests

13.3. Interactive Information Requests

13.3.1. Interactive Information Requests sent on Click or tap to enter a date.

14.APPENDIX B (CONSULTANT MEMOS)

14.1. Human Factors Review Memo – Insert Consultant Name
14.2. Clinical Review Memo – Insert Consultant Name
14.3. Insert Discipline Review Memo – Insert Consultant Name