CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761224Orig1s000

OTHER REVIEW(S)

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:	December 8, 2021
To:	Linda Ebonine, PA-C Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TEZSPIRE (tezepelumab-ekko)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761224
Applicant:	AstraZeneca Pharmaceuticals LP (AstraZeneca)

1 INTRODUCTION

On May 7, 2021, AstraZeneca Pharmaceuticals LP (AstraZeneca), submitted for the Agency's review, original Biologics License Application (BLA) #761224 TEZSPIRE (tezepelumab-ekko) injection. This BLA proposes an indication for the add-on maintenance treatment of patients aged 12 years and older with (b) (4) (b) (4) severe asthma, (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonology, Allergy, and Critical Care (DPACC) on December 1, 2021, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TEZSPIRE (tezepelumab-ekko) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft TEZSPIRE (tezepelumab-ekko) PPI received on May 7, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 1, 2021.
- Draft TEZSPIRE (tezepelumab-ekko) Prescribing Information (PI) received on May 7, 2021, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 1, 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%.

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

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI 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 PPI.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
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DMPP-OPDP review of tezepelumab-ekko (TEZSPIRE) BLA 761224 PPI

KYLE SNYDER
12/08/2021 01:29:41 PM

MARCIA B WILLIAMS
12/08/2021 01:31:12 PM

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

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

Memorandum

Date: December 8, 2021

To: Linda Ebonine, Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care

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

CC: Twyla Thompson, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for TEZSPIRE™ (tezepelumab-ekko) injection, for subcutaneous use

BLA: 761224

In response to DPACC's consult request dated December 1, 2021, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original BLA submission for TEZSPIRE™ (tezepelumab-ekko) injection, for subcutaneous use.

Labeling: OPDP's comments on the proposed PI are based on the draft labeling received by electronic mail from DPACC on December 1, 2021, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI, and comments 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 May 7, 2021, and we do not have any comments.

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

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/s/

KYLE SNYDER
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Clinical Inspection Summary

Date	December 6, 2021
From	Tina Chang, M.D., Reviewer Karen Bleich, M.D., Team Leader Kassa Ayalew, M.D., M.P.H, Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Jennifer Lan, M.D., Clinical Reviewer Miya Paterniti, M.D., Clinical Team Leader Linda Ebonine, PA-C, Regulatory Project Manager Division of Pulmonology, Allergy, and Critical Care (DPACC)
BLA #	761224
Applicant	AstraZeneca
Drug	TEZSPIRE (tezepelumab)
NME (Yes/No)	Yes
Therapeutic Classification	Anti-thymic stromal lymphopoietin (TSLP) human monoclonal antibody (gG2λ)
Proposed Indication(s)	Indicated for the add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma (b) (4)
Consultation Request Date	June 4, 2021
Summary Goal Date	November 15, 2021 (Original); December 6, 2021 (Extension)
Action Goal Date	December 17, 2021
PDUFA Date	January 7, 2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from two studies (CD-RI-MEDI9929-1146 and D5180C00007) were submitted to the Agency in support of a Biologics Licensing Application (BLA) 761224 for tezepelumab for the add-on maintenance treatment of patients aged 12 years and older with (b) (4) (b) (4) severe asthma. (b) (4) Clinical inspections of Drs. Martti Antila, Jeremy Cole, David Fuentes, Oleg Kraydashenko, Vasyl Melnyk, and Selwyn Spangenthal, and AstraZeneca were conducted in support of this application.

OSI has significant concerns regarding the reliability of the data generated by Dr. Melnyk because of his failure to maintain most of the source records for study CD-RI-MEDI9929-1146, and implausible spirometry results, according to a QC review by the spirometry vendor, ERT. Therefore, OSI recommends a sensitivity analysis to assess the validity and robustness of the results from the primary analysis and lung function analyses by excluding the data generated by Dr. Melnyk.

The clinical inspections of Drs. Jeremy Cole, David Fuentes, Oleg Kraydashenko, Selwyn Spangenthal, AstraZeneca, and the remote regulatory assessment of Dr. Martti Antila demonstrated no significant findings. Protocols CD-RI-MEDI9929-1146 and D5180C00007 appear to have been conducted adequately and the data generated by the clinical investigators (other than Dr. Melnyk) appear acceptable in support of the proposed indication.

II. BACKGROUND

Tezepelumab is an anti-thymic stromal lymphopoietin (TSLP) human monoclonal antibody (gG2λ) proposed for the add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma, (b) (4)

Protocol CD-RI-MEDI9929-1146 (Pathway)

Study Title: A Phase 2 Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of MEDI9929 in Adult Subjects with Inadequately Controlled, Severe Asthma

Primary Objective: To evaluate the effect of three dose levels of tezepelumab on asthma exacerbations in adult subjects with inadequately controlled, severe asthma.

Primary Endpoint: Annual asthma exacerbation rate over 52 weeks.

Definition of an asthma exacerbation: a worsening of asthma that led to any of the following:

- Use of systemic corticosteroids for at least 3 days.
    - A single depo-injectable dose of corticosteroids was considered equivalent to a 3-day course of systemic corticosteroids.
    - For subjects receiving maintenance oral corticosteroids (OCS) a temporary doubling of the maintenance dose for at least 3 days qualifies.
- An emergency room visit due to asthma that required systemic corticosteroids for at least 3 days.
- An inpatient hospitalization due to asthma.

An ePRO device was to be given to subjects to detect worsening of asthma, defined as new or increased symptoms and/or signs (examination of lung function) that could be either concerning to the subject (subject-driven) or related to an Asthma Daily Diary alert (diary-driven) via the ePRO device. The ePRO device will be programmed to alert both the subject and study center when certain pre-specified (objective) asthma-worsening thresholds are crossed including:

- Decrease in morning peak flow ≥ 30% on at least 2 of 3 successive days compared with baseline (last 7 days of run-in), and/or

- A ≥ 50% increase in rescue medication (minimum increase of 2 or more puffs, or one

new or additional nebulized β2 agonist) on at least 2 of 3 successive days compared with the average use for the previous week, and/or

- Nocturnal awakening due to asthma requiring rescue medication use for at least 2 of 3 successive nights, and/or

- An increase in total asthma symptom score (the sum of daytime [evening assessment] and nighttime [morning assessment]) of at least 2 units above the screening/run-in period average (last 10 days of screening/run-in), or the highest possible score (daily score of 6), on at least 2 of 3 successive days

The clinical investigator was to determine whether an asthma worsening event is an asthma exacerbation. If an exacerbation event is not associated with deterioration in at least one of the pre-specified objective measurements (e.g., exacerbation event is subject-driven), the investigator will indicate on the electronic case report form (eCRF) any other objective measures that were used in their decision to classify this asthma worsening event as an asthma exacerbation. Events that the investigator believes are exacerbations but are not supported by any specified objective assessment will be reviewed by an independent adjudication committee to determine if they are a medically valid asthma exacerbation.

Subjects with severe uncontrolled asthma were to be randomized in a 1:1:1:1 ratio to receive one of three doses of tezepelumab or placebo subcutaneously for 52 weeks as add-on maintenance therapy as follows:

- 70 mg every 4 weeks
- 210 mg every 4 weeks
- 280 mg every 2 weeks
- Placebo every 2 weeks

*The 210 mg dose is the dose of interest for the Review Division.

Prior to randomization, subjects were to be stratified by study site, then by blood eosinophil account and by inhaled corticosteroid (ICS) dose level (medium or high) to ensure that at least 40% of subjects would be taking high-dose ICS. Subjects taking maintenance oral corticosteroids were to be automatically assigned to the high-dose ICS strata.

The first subject was enrolled on 19 December 2013 and the last subject completed the study 1 March 2017. 97 study centers randomized subjects in 12 countries (USA, Slovakia, Bulgaria, Czech Republic, Hungary, Israel, Japan, Latvia, Lithuania, Serbia, South Africa, and Ukraine).

Protocol D5180C00007 (Navigator)

Study Title: A Multicentre, Randomised, Double-Blind, Placebo Controlled, Parallel Group, Phase 3 Study to Evaluate the Efficacy and Safety of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma

Adult and adolescent subjects with severe uncontrolled asthma were to be randomized 1:1 to tezepelumab 210 mg or placebo every 4 weeks subcutaneously from Day 0 to Week 48 as add-

on maintenance therapy.

Primary Objective: To assess the effect of 210 mg tezepelumab SC Q4W on asthma exacerbations in adult and adolescent subjects with severe uncontrolled asthma compared with placebo.

Primary Endpoint: Annual asthma exacerbation rate over 52 weeks between treatment groups. The definition of an asthma exacerbation are the same as in study CD-RI-MEDI9929-1146 except for the following:

- An emergency room or urgent care visit is defined as evaluation and treatment for <24 hours in an emergency department or urgent care center instead of for at least 3 days.

The ePRO programming and procedures to detect asthma worsening are the same as in study CD-RI-MEDI9929-1146 for the criteria regarding an increase in total asthma symptoms score criteria. The rest of the criteria are different from those listed in study CD-RI-MEDI9929-1146 and are the following:

- A decrease in morning peak flow ≥20% on at least 2 consecutive days compared with baseline.

- An increase in rescue medication use of 4 or more puffs on at least 2 consecutive days compared with the average use during baseline or use of 12 puffs/day on any one day, and/or

- An additional nebulized β2 agonist use on at least 2 consecutive days compared with the average use during baseline, and/or

- An increase of 2 or more nights with awakenings due to asthma requiring rescue medication over a 7-day period compared with the average during baseline, and/or ≥ 6 out of previous 7 nights with awakenings due to asthma requiring rescue medication (this criteria should be met on 2 consecutive days).

If an exacerbation event is not associated with deterioration in at least 1 of the pre-specified objective measurements, the Investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF. Events that are not supported by any objective assessment will be deemed not to be a protocol-defined exacerbation.

An independent adjudication committee will evaluate cases of ER or urgent care visits and hospitalizations that occur from randomization up to the end of treatment period, as well as all deaths from randomization until the end of follow up period, to evaluate whether any such event is due to a worsening of asthma.

The first subject was enrolled on 23 November 2017, and the analyses presented in the clinical study report are based on a database lock date of 29 October 2020. The last subject completed the study on 9 September 2020. The study was conducted in 231 centers in 17 countries.

Rationale for Site Selection

The clinical investigators Drs. Martti Antila, Jeremy Cole, David Fuentes, Oleg Kraydashenko, and Vasyl Melnyk were selected for surveillance inspections using risk-based approach that considers numbers of enrolled subjects and treatment effect. Dr. Melnyk was also selected due to having a history of a complaint of alleged falsification, including concerns pertaining to [redacted] (b) (4) data for a different study not part of this application [redacted] (b) (4) For this current application, during Dr. Melnyk's inspection, it was discovered that Dr. Melnyk failed to retain most source records for the Phase 2 study CD-RI-MEDI9929-1146. A sponsor inspection was subsequently recommended to further evaluate study oversight by the sponsor. Because the data generated by Dr. Melnyk's site is considered unreliable, the clinical team requested an additional CI inspection to assess conduct of study CD-RI-MEDI9929-1146. Dr. Selwyn Spangenthal was selected for the additional clinical site inspection due to high enrollment.

III. RESULTS (by site):

1. **Dr. Martti Antila**
   Clinica De Alergia Martti Antila S/S Ltda
   Duque De Caxias, 119- Vila Leao
   18040-425, Sorocaba/SP Brazil
   Study D5180C00007 (Navigator), Site 710
   Remote Regulatory Assessment (RRA) Dates: August 11 – September 9, 2021

A remote regulatory assessment (in lieu of a full Clinical Investigator GCP site inspection) was conducted for this site due to travel restrictions during the COVID-19 pandemic. Videoconferencing via Zoom.Gov and document sharing via Box.com were used to exchange information.

Dr. Martti Antila has not been previously inspected.

For study D5180C00007, Dr. Antila screened 63 subjects and randomized 31 subjects. Of the 31 randomized subjects, 30 subjects completed the study. Records related to the primary efficacy endpoint data for 18 subjects were reviewed during the RRA.

This RRA was limited due to time constraints related to the requirement for the Brazilian National Ethics Committee (EC) to approve the sharing of subject medical records via Box.com. The first attempt at an opening meeting for the RRA was on August 11th, 2021, but the site communicated that the subject records could not be shared as they were still waiting for approval. The first full RRA call took place on August 26th and reviewed investigator site file

contents and sponsor-provided ePRO data. The RRA also reviewed enrollment logs, informed consent log, investigational product accountability log, monitoring visit log, visit reports, and protocol deviation log. Once access to subject medical records was approved by the EC, there was only time to review the primary efficacy endpoint data. Eligibility data, informed consent, reporting of adverse events, case report forms, concomitant medications, and financial disclosure forms were not reviewed.

The primary efficacy endpoint data for the total number of asthma exacerbation events over 52 weeks were verified for 18 subjects by comparison of source record documents at the site to the submitted subject data line listings. Dr. Antila appeared to follow the protocol adequately. There was a limited review of safety consisting of comparison of the site's adverse event log to the reported events in the data line listings and these documents matched each other.

2. **Dr. Jeremy Cole**
   Ok Clinical Research
   120 N. Bryant
   Suite 100
   Edmond, OK 73034
   Study D5180C00007 (Navigator), Site 7822
   Clinical Inspection dates: June 21-24, 2021

Dr. Cole was previously inspected on 2/28/18 and classified as NAI.

For study D5180C00007, Dr. Cole screened 21 subjects and randomized 19 subjects. Of the 19 randomized subjects, 19 subjects completed the study. Records for all 21 subjects were reviewed during the inspection.

The inspection reviewed the overall control and administration of the clinical trial, adherence to study protocols, IRB documentation, subject records, financial disclosures, study monitoring, adverse event reporting, protocol deviation reports, clinical source data, signed investigator statements, and study drug accountability.

The primary efficacy endpoint data for the total number of asthma exacerbation events were verified for all subjects by comparison of source documents at the site to the submitted subject data line listings. There was no evidence of underreporting of adverse events.

The clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

3. **Dr. David Fuentes**
   Tts Research
   1420 River Road, Suite 100
   Boerne, TX 78006
   Study D5180C00007 (Navigator), Site 7904
   Clinical Inspection Dates: August 16-19, 2021

Dr. Fuentes has been previously inspected on 10/18/19 and classified as VAI for enrolling two ineligible subjects into the study (prohibited medication usage).

For study D5180C00007, Dr. Fuentes screened 39 subjects and randomized 17 subjects. Of the 17 randomized subjects, 16 subjects completed the study. Records for 39 subjects were reviewed during the inspection.

The inspection reviewed the overall control and administration of the clinical trial, adherence to study protocols, IRB documentation, subject records, financial disclosures, study monitoring, protocols with their amendments, signed investigator statements, protocol deviation reports, adverse event reporting, clinical source data, and study drug accountability.

The primary efficacy endpoint data for the total number of asthma exacerbation events were verified for all subjects by comparison of source documents at the site to the submitted subject data line listings. There was no evidence of underreporting of adverse events.

The clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

4. **Dr. Oleg Kraydashenko**
   Zaporozye City Clinical Hospital #6 Therapy Dept.
   34 Stalevariv St.
   Zaporizhzhia, NA 69035
   Ukraine
   Study CD-RI-MEDI9929-1146 (Pathway), Site 2000290
   Clinical Inspection Dates: September 6-10, 2021

Dr. Kraydashenko has not been previously inspected.

For study CD-RI-MEDI9929-1146, this site screened 33 subjects and randomized 26 subjects. Among the 26 randomized subjects, 25 subjects completed the study. Records for 26 subjects were reviewed during the inspection pertaining to eligibility, adverse events and primary efficacy endpoint data.

The inspection reviewed ethics committee approvals, financial disclosure forms, training records, informed consent forms, pharmacy binders, and subject records.

The primary efficacy endpoint data for the total number of asthma exacerbation events were verified for all 26 enrolled subjects by comparison of source documents at the site to the submitted subject data line listings.

Within the subject data listings, it was noted that the number of asthma exacerbations reported under “Adverse Events” (n=6) were different for the “Total Number of Exacerbations” (n=3) reported for the primary endpoint for Subject 002 randomized to the placebo group.

Reviewer's comment: We do not know if this discrepancy is an isolated event or if it occurred at non-inspected sites. If more subjects are affected, then it could potentially impact the primary endpoint assessment. This issue was discussed with the review division, and an IR was sent to the sponsor inquiring if any other similar discrepancies can be found in other subjects or sites with an explanation for this discrepancy.

The clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

5. **Dr. Vasyl Melnyk**
   121/3 Kharkivske Shose St., Kyiv City
   Tuberculosis Hospital #1 with Disp Dept
   Dept Of Dd Of Rod Phei Kyiv Mu of
   Uapm, Kyiv, UA
   Ukraine
   Study CD-RI-MEDI9929-1146 (Pathway), Site 2000366
   Clinical Inspection Dates: September 9-13, 2021

Dr. Vasyl Melnyk has not been previously inspected.

For study CD-RI-MEDI9929-1146, this site screened 25 subjects and randomized 22 subjects. Among the 22 randomized subjects, 21 subjects completed the study. Records for six subjects (Subjects# (b) (6)) were reviewed.

Dr. Melnyk's inspection was limited because he was not able to locate all subject records for this inspection, and source documents for only six subjects were available. The inspection reviewed medical records, adverse events and concomitant medications, electrocardiogram tracings and reports, laboratory and PFT reports, subject diary alerts, and IWRS confirmation for these six subjects. The remaining 16 subject records were incomplete in that they were missing all pulmonary function testing reports, eligibility documents, visit notes, concomitant medications, adverse events, and primary endpoint data. The informed consent forms for all subjects, the records for the three screen failures, patient identification log, and the hardcopy record of eCRF data file were not available for review. The primary efficacy endpoint data for the total number of asthma exacerbation events were verified for the six subject records that were available (Subjects# (b) (6)).

Reviewer's comment: We are unable to verify the reliability of the data including subject eligibility, adverse events, and primary endpoint data for a majority of the subjects (n=16). Per CFR 312.62. Dr. Melnyk failed to retain all study related records for a period of 2 years following the date a marketing application is approved for the indication for which it is being investigated. A sponsor inspection was conducted to understand if the sponsor maintained adequate oversight of the clinical trial and adequate monitoring of Dr. Melnyk's site. An additional CI inspection of Dr. Selwyn Spangenthal was conducted to gather further

information about study conduct for study CD-RI-MEDI9929-1146. Please see the results below.

In January 2016, spirometry issues were identified at this site by [redacted] who was contracted by the sponsor as the central reader for PFT results. [redacted] reported inadequate spirometry results for more than 120 visits with end of test errors, and the most common issue being abrupt termination of expiratory flow/effort. In February 2016, the sponsor requested that the Overread department look at all the PFT data from Dr. Melnyk's site and on February 24, 2016, a monitoring visit was conducted to review the spirometry issues at this site. A detailed review of the spirometry data which included more than 424 measurements was performed and summarized in [redacted] Quality Control Review of Spirometry Data, dated 15 March 2016. Problems were identified with almost every patient enrolled at this site including an abrupt termination of expiratory flow, sharp reduction in effort within the first second of forced exhalation and inspiration to a submaximal lung volume prior to the FVC maneuver, and many sessions showing multiple problems in the same effort repeated without improvement in the session. Additional comments include the technician rushing the test subject through maneuvers (5-8 maneuvers in as little as 3 minutes) and very high and improbable FEV1/FVC ratios at 98-99%, FEV1 is not repeatable. Also, [redacted] noted that "several of the measurements for different subjects appeared similar in morphology." One example explained in the report include details pertaining to the FVC, FEV1, PEFR, and expiratory flow-volume curve morphology show a very close match between subject [redacted] labeled V2 Optional PFT dated [redacted] and Subject [redacted] labeled V30, Post PFT, dated [redacted] In terms of the FEV1, which is an efficacy outcome reported in the draft drug labeling, the [redacted] report states the results should be excluded for 5 of the enrolled subjects based on the abnormalities demonstrated in their analysis. Additionally, [redacted] reports that the coefficient of variation for the FEV1 for all of the remaining subjects is less than what would be expected as a coefficient of variation for a single subject with normal lung function.

Reviewer's comment: The PFT data/results from Dr. Melnyk's site may impact eligibility and one of the secondary efficacy endpoints included in the draft product labeling. PFTs were delegated appropriately to sub-investigators who were qualified in training and education to do PFTs. Dr. Melnyk believed the device was malfunctioned and that it was not due to the performer. However, [redacted] states in their report that they believe the system was running properly and believed the errors to be related to handling issues. In response to [redacted] report/review, a site visit was recommended so that the operators could demonstrate their pulmonary function technique. The site was re-trained on spirometry technical skills on April 7, 2016. However, this study was completed in 2017, [redacted] Dr. Melnyk discontinued participating in research in 2019, currently not involved in any studies and has no intention on participating in any future studies. Because we do not know how the sponsor made their decisions about Dr. Melnyk's [redacted] QC report or if other QC reports were performed for other sites, the review division may consider sending an IR to the sponsor to

obtain more information about the sponsor's assessment of the reliability of the spirometry data, including (b) (4) *QC reports for other sites (if any).*

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for regulatory violation related to the described findings. A Warning Letter will also be issued to Dr. Melnyk. Based on the inspection findings, the data submitted by Dr. Melnyk is considered unreliable.

6. **Dr. Selwyn Spangenthal**
   American Health Research
   8045 Providence Road, Suite 300
   Charlotte, NC 28207
   Study CD-RI-MEDI9929-1146 (Pathway), Site #2000161 and #2000723
   Clinical Inspection Dates: November 3-8. 2021

Dr. Spangenthal was previously inspected from April 15-18, 2019 and was classified as No Action Indicated (NAI).

Dr. Spangenthal opened Clinical Research of Charlotte (Site #20073) in April 2000 and then opened the American Health Research (Site #2000161) in February 2002, and both businesses operated out of the same physical location at 8045 Providence Road, Charlotte, NC.

For Study CD-RI-MEDI9929-1146, Dr. Spangenthal screened 15 subjects and randomized three subjects at study site #200161. All three subjects completed the study. Dr. Spangenthal also screened 14 subjects and randomized eight subjects at site #2000723. Among the eight randomized subjects, 6 subjects completed the study.

The inspection reviewed the informed consent forms, IRB submissions and approvals, correspondence, monitoring, investigational product accountability and storage, training, FDA 1572s, site responsibility delegation, financial disclosures, subject enrollment, subject records, adherence to protocol, adverse event reporting, concomitant medications reporting, case report form, data listings, laboratory testing, and ECGs.

Primary efficacy endpoint data were reviewed for 11 subjects which included three subjects at study site #200161 and eight subjects at site #2000723 and no discrepancies were noted when comparing the source documents at the site with the submitted subject data listings.

Two unreported adverse events were identified during the review of the source records. Associated with these two adverse events, there were also two unreported concomitant medications, as described in the table below. In both cases, the clinical investigator did not transcribe the two adverse events or the two concomitant medications in the eCRF.

Table 4. Unreported Adverse Events and Concomitant Medications

Subject #/ Treatment Arm	Start Date of Study	Primary Endpoint Assessment	Adverse Event	Start Date of Adverse	Concomitant Medication	Dates of Concomitant Medication

	Drug	(Week 52)		Event		
2000723- (b) (6) 210 mg	(b) (6)		Virus	(b) (6)	Ibuprofen 400 mg every six hours	(b) (6)
2000723- (b) (6) 70 mg			Mild Common Cold		Nyquil 30 mL x 1	

Reviewer's comments: There is no evidence of subject harm. The unreported concomitant medications are not restricted per the protocol. The unreported adverse events and concomitant medications are listed above for the review division's consideration.

The clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

7. **AstraZeneca PLC**
   One Medimmune
   Gaithersburg, Maryland 20878
   Clinical Inspection Dates: September 22-30, 2021

AstraZeneca was previously inspected on February 26, 2021 and classified as a NAI.

This sponsor inspection was added due to the missing study documentation at Dr. Melnyk's clinical site to further understand if the sponsor maintained adequate oversight of the clinical trial.

Dr. Melnyk's site received 18 site monitoring visits between December 2014 and December 2016 plus 13 additional monitoring visits for the pharmacy for IP integrity and accountability. The site was place on recruitment hold on 15 May 2016 due to an erroneously manually generated IP re-supply request by the site. All monitoring reports for this site was reviewed and included information pertaining to enrollment, ICF verification, source data verification, protocol deviations, SAEs, IP control and accountability, adequacy of facilities and equipment, and site staff training and PI oversight.

Reviewer's comments: Based on the review of the monitoring reports for Dr. Melnyk, the sponsor appeared to have monitored Dr. Melnyk's site in accordance with their monitoring plan and CRO procedures., There was no indication of missing records or unresolved critical issues found during monitoring.

Ten sites, sites #238 (Bukovskis), #243 (Stonkus), #290 (Kraydashenko), #363 (Nishikawa), #366 (Melnyk), #996 (Markova), #286 (Dziublyk), #302 (Savchenko), #445 (Gyrina), and #446 (Molodtsov), were randomly selected for review of monitoring documents for study CD-RI-MEDI9929-1146 (Pathway) and six sites, sites #0204 (Delgado Vizcarra), #6206 (Vasilev), #7703 (Lapshyn), #7822 (Cole), #0710 (Antila), and #7904 (Fuentes), were randomly selected for review of monitoring documents for study D5180C00007 (Navigator). Among these 16

sites, one site #286 (Dziublyk) showed a recurring pattern of major protocol deviations resulting in a focused site visit that discovered that the observed issues of missing lab results before randomization (qualified for randomization results are received after subject is randomized); no regular follow up of ePRO compliance; and mistakes with stratification in IVRS were largely due to lack of resources. The sponsor stopped recruitment at this site, retrained all site staff on the protocol, and increased site monitoring visits from a visit every 16 weeks to a every six weeks, and the site staff was able to return to the expected compliance level with a decrease in protocol deviations.

Reviewer's comments: Among the monitoring documents reviewed for 16 sites, it appeared that the sponsor's monitoring of investigator sites was adequate and appropriate steps were taken by the sponsor to bring noncompliant sites into compliance.

In general, the sponsor appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was not issued. Data submitted by this sponsor appear acceptable in support of this biologic license application.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: *{See appended electronic signature page}*

Kassa Ayalew, M.D., M.P.H.

Division Director
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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/s/

SUYOUNG T CHANG
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KAREN B BLEICH
12/06/2021 03:21:42 PM

KASSA AYALEW
12/06/2021 03:31:14 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	November 9, 2021
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	BLA 761224
Product Name and Strength:	Tezspire (tezepelumab-ekko) injection, 210 mg/1.91 mL (110 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AstraZeneca AB
FDA Received Date:	May 7, 2021 and October 21, 2021
OSE RCM #:	2021-1005
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Tezspire (tezepelumab-ekko) injection, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Tezspire prescribing information (PI), container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 CONCLUSION AND RECOMMENDATIONS

The proposed container labels and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for AstraZeneca AB.

4 RECOMMENDATIONS FOR ASTRAZENECA AB

Table 2. Identified Issues and Recommendations for AstraZeneca AB (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s)			
1.	The quantity and dosage form are omitted from the container labels	This may cause confusion or difficulty readily locating safety information	On the vial label add the following: "1 Single-dose vial Discard unused portion" On the Pre-filled syringe label add the following: "1 single-dose pre-filled syringe Discard unused portion"
Container Label(s) and Carton Labeling			
1.	The labels and labeling contain placeholders for the proprietary name and suffix	The proprietary name and suffix have been conditionally approved[ab] since submission of the labels and labeling and should be updated accordingly.	Revise the placeholder 'Tradename' and 'tezepelumab-xxxx' to the respective conditionally approved name and suffix: 'Tezspire (tezepelumab-ekko)'
Carton Labeling			
1.	The Usual dosage reads as "Usual Dosage: See Prescribing Information"	Lacks consistency with the prescribing information	To ensure consistency with the Prescribing Information, revise the statement, (b) (4) to read "Recommended Dosage: See prescribing information."
2.	The vial carton is missing storage information that is present on the pre-filled syringe carton	Lacks consistency with section 16 'Storage and Handling' in the prescribing information	To ensure consistency with the Prescribing Information, add the statement "If needed Tezspire may be stored at

[a] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80619446&_afrRedirect=1532857738079889

[b] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805febac&_afrRedirect=1532952012091976

Table 2. Identified Issues and Recommendations for AstraZeneca AB (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			room temperature between 68°F to 77°F (20°C to 25°C) for maximum of 30 days. Once stored at room temperature, do not place in refrigerator. Discard after 30 days." Date removed from refrigerator: ___/___/___.
3.	The information stating to not use if the security seal has been broken is omitted from the carton	Lacks consistency with section 2.2 in the prescribing information	To ensure consistency with the Prescribing Information, add the statement "Ensure the security seal has not been broken prior to use"

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Tezspire that AstraZeneca AB submitted on October 21, 2021.

Table 3. Relevant Product Information for Tezspire	
Initial Approval Date	N/A
Active Ingredient	tezepelumab-ekko
Indication	add-on maintenance treatment of adult and pediatric patients aged 12 years and older with (b) (4) severe asthma
Route of Administration	subcutaneous
Dosage Form	injection
Strength	210 mg/1.91 mL (110 mg/mL)
Dose and Frequency	210 mg administered once every 4 weeks
How Supplied	sterile, preservative-free, clear to opalescent, colorless to light yellow solution supplied as a single-dose vial or single-dose pre-filled syringe with a fixed 27-gauge ½ inch needle with a needle cover
Storage	refrigerated between 36°F to 46°F (2°C to 8°C). If necessary, TEZSPIRE may be kept at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum of 30 days

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Tezspire labels and labeling submitted by AstraZeneca AB.

- Container label(s) received on May 7, 2021
- Carton labeling received on May 7, 2021
- Professional Sample Container label(s) received on May 7, 2021
- Professional Sample Carton Labeling received on May 7, 2021
- Prescribing Information (Image not shown) received on October 21, 2021, available from \\CDSESUB1\evsprod\bla761224\0029\m1\us\nonannotated-draft-label-tezepelumab-uspi.pdf

F.2 Label and Labeling Images

Container label(s)

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

4 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/s/

LISSA C OWENS
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IDALIA E RYCHLIK
11/10/2021 11:38:49 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – PRE-FILLED SYRINGES

Date	06/07/2021		
To:	Anita Brown		
Requesting Center/Office	CDER/OPQ	**Clinical Review Division**	OPRO/DRBPMI/RBPMB1
From	Michaela Schulman OPEQ/OHT3/DHT3C		
Through (Team)	Suzanne Hudak, Acting Injection Devices Team Lead OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	ICCR: 2100501 ICC: BLA 761224 Submission: Case 00724194 Sponsor: AstraZeneca Drug/Biologic: Tezepelumab Indications for Use: The add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma (b) (4)		
Recommendation	**Final Recommendation: 10/5/2021** ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with the following Post-Market Requirements/Commitments, ☐ Device Constituent Parts of the Combination Product are Not Approvable with the following CR Deficiencies		
	Comments to Review Team: N/A		
	PMC/PMR or CR Deficiencies: N/A		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. PURPOSE

This review provides an assessment of the needle safety device constituent part[1] of the prefilled syringe product.

This review will cover the following review areas:

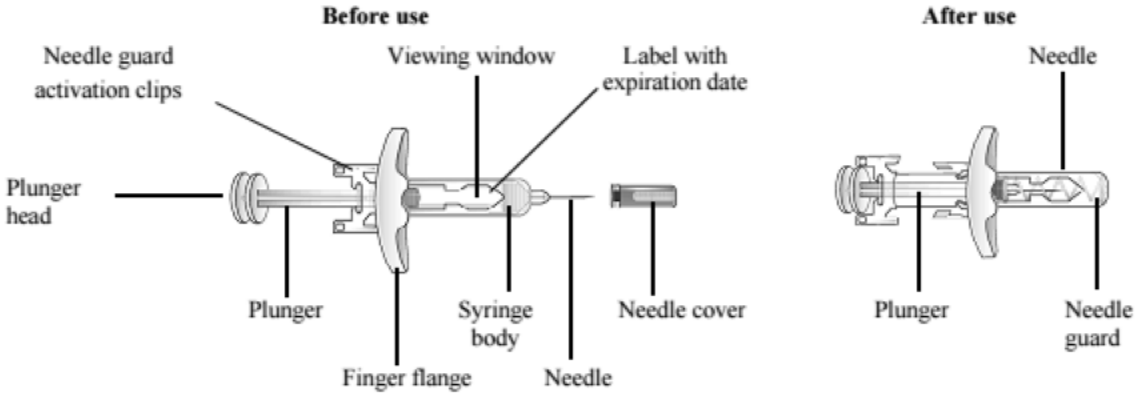
☒ Needle safety device constituent performance [1]
☒ Needle safety Stability
☒ Needle safety Control strategy

CDRH Quality Systems Assessment / Facilities consult not required per internal MAP 5017.7

It was determined that a device quality systems / facilities assessment is not required for this product because the product is not an emergency (i.e., life-saving and essential[2]) treatment that are administered by non-health care professionals.

The combination product is indicated for the add-on maintenance treatment of patients aged 12 years and older with (b) (4) severe asthma. (b) (4) The drug is administered by a healthcare professional subcutaneously once every 4 weeks.

2. DEVICE DESCRIPTION



Requirement	Describe
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	Healthcare professional
Injection Site	Upper arm, thigh or abdomen
Injection tissue and depth of injection	Subcutaneous
Needle connection (e.g. luer, slip tip, staked)	Staked
Needle safety type (active or passive)	Active
Delivered Dose Volume	1.91 mL

[1] The scope of this review will be limited to the device constituent performance in accordance with ISO 23908:2011 Sharps Injury Protection and FDA guidance Medical Devices with Sharps Injury Prevention Features. Therefore, for a PFS with a needle safety device constituent the review will be limited to needle safety performance requirements and will not cover functions of the primary container (container content, breakloose force, glide force, needle shield removal force, etc.,).

[2] Examples of emergency, life-saving and essential treatments include those used for conditions such as anaphylaxis or cardiac arrest and others in which failure of drug delivery may expose the patient to the reasonable likelihood of serious injury or death.

Shelf-life/Storage, including excursions (e.g., (b) (4) months, 5C)	(b) (4) months at 5°C

3. FILING REVIEW

Checklist	Present		
Item	**Yes**	**No**	**N/A**
Device Description	X		
Letters of Authorization	X		
Design Verification Summary and reports for needle safety attributes • Shelf-life • Shipping • Free-Fall	X		
Design Validation of needle safety EPRs (See Section 4.2)	X		
Control Strategy of needle safety EPRs	X		

4. DEVICE PERFORMANCE REVIEW

The APFS is designed to deliver 1.91 mL for subcutaneous manual injection. The glass barrel meets USP (b) (4) (b) (4) quality standards and is delivered by the supplier (b) (4) The interior of the syringe barrel is siliconized for smooth gliding of the plunger stopper during administration. The prefillable syringe barrel is provided with a ½-inch 27 gauge, special thin-wall staked needle. The APFS is provided to the user fully assembled with a plunger rod and extended finger flange.

Figure 4 and Figure 3 below show the PFS with Needle Safety Device. Table 2 includes the components and materials.

Figure 4 Schematic of an Exploded View of the APFS

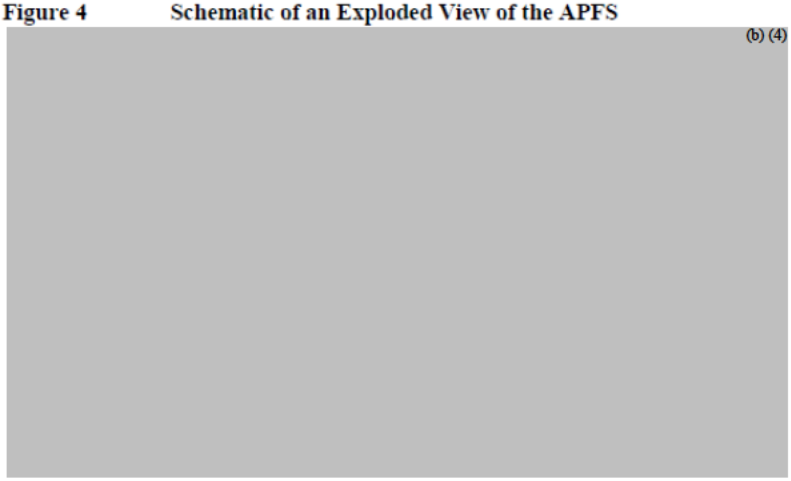


Figure 3 Accessorized Prefilled Syringe (APFS)

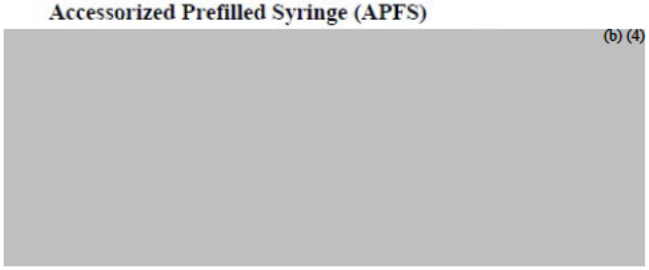


Table 2 Components and Materials of APFS

Component	Material Description	Color	Contact Type with Human Body
Needle	27 Gauge (b) (4) ½" stainless steel needle	NA	Direct
Glass Barrel (DMF (b) (4))	2.25mL long (b) (4) glass syringe barrel with silicone oil lubricant	Transparent	Indirect
Rigid Needle Shield	Made of (b) (4) housing plus needle-shield elastomer	Grey	Direct
Plunger Stopper	(b) (4) elastomer (b) (4) (b) (4)	Grey	Indirect
Needle Guard	Body and guard made of (b) (4)	Transparent	Direct
	Spring made of stainless steel	NA	No contact
Extended finger flange	(b) (4)	White	Direct
Plunger Rod	(b) (4)	White	Direct

NA = not applicable; (b) (4)

The sponsor clarified that there are design changes from the clinical and commercial design. The change is only with the NSD. The NSD is changing from the (b) (4) to the (b) (4) (b) (4) incorporates an updated design for the needle guard, extended finger flange and plunger rod. All other components remain unchanged. Figure 5 and Table 3 below demonstrate the differences between the two. The sponsor specified that the functional requirements of the combination product remain unchanged and use steps are identical between the two devices. The full design and development activities were performed on the commercial combination product configuration.

Table 3 Comparison of Clinical to Commercial APFS

	Clinical Process	Commercial Process
Manufacturing site	(b) (4)	
Deliverable volume	1.91 mL	
Primary container	(b) (4) 2.25 mL syringe, ½ inch 27-gauge (b) (4) needle, Rigid Needle Shield	
Primary closure	(b) (4) plunger stopper (b) (4)	
APFS Components	(b) (4) platform including: Extended finger flange (b) (4) (b) (4) Needle Guard (b) (4) Plunger Rod (b) (4)	(b) (4) platform including: Extended finger flange (b) (4) (b) (4) Needle Guard (b) (4) Plunger (b) (4) Rod

Figure 5 Comparison of the APFS with (b) (4) Needle Safety Device Design

(b) (4)

Component colors are not representative of a to-be-marketed or clinical configuration.

4.1. Design Verification & Validation

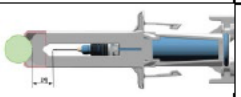
Performance Requirement	Specification	Verification Method Acceptable (Y/N)	Validation (Y/N)	Shelf-life (Y/N)	Shipping/ Transportation (Y/N)	Drop/Free Fall Testing (Y/N)
Needle Safety Activation force	(b) (4) N	Y – N=30 per aging point (before shipping, after shipping, after accelerated aging), performed (b) (4)	Y – Simulated Use study where 8 participants were requested to simulate 64 injections each	5 years at 25 ± 3°C/60% ± 5% RH; 6 days at 50 ± 2°C (performed (b) (4)	Y (performed (b) (4)	Y – performed per ASTM D4169
Needle Safety Activation Force – Shipping	Visual	N=59	*N/A*	*N/A*	Y, ASTM 4169	*N/A*
Needle safety lockout force/override force/safe mode challenge	(b) (4) N (performed by (b) (4))	N=100 (per aging point e.g. before shipping, after shipping and after accelerated aging) for a total of N=300 performed (b) (4)	Y	5 years accelerated aging (performed (b) (4) Lockout confirmation n=299 (performed by AstraZeneca)	Y Lockout confirmation n n=299 (performed by AstraZeneca)	Y
Needle safety Access in safe mode	A sphere having a radius of 6 mm (simulating a fingertip) shall not contact the extremity of the needle point or sharps when positioned against the safety feature	 Y – ISO 23908:2011	6 mm sphere is pressed against aperture of the device. The sphere is still 4.92 mm from the needle tip	*N/A*	*N/A*	*N/A*

Table 3 APFS Performance Over Intended Shelf Life

Data Source	Description	Data	Presentation	PFS-SA Configuration
Data Source #3 NSD aging study (b) (4)	Functional testing on commercial (b) (4) (b) (4) conducted (b) (4) after accelerated aging with commercial APFS components Refer to Module 3, Section 3.2.P Medical Devices and DMF (b) (4) for results. Letter of Authorization provided in Module 1.	NSD Activation Force	Commercial NSD with commercial APFS components	(b) (4) 27G (b) (4) needle

The sponsor clarified that design verification was performed in the following order: 1) pre-conditioning, 2) environmental tests and 3) physical testing. Tables 5, 6 and 7 illustrate each step.

Table 5 Description of Pre-conditions

Pre-condition	Description
Aging	The combination product is placed in a chamber for 36 months at a temperature of 5°C ± 3°C, no humidity requirement.
Simulated shipping	After being packaged into a shipper box, the labeled and packaged combination product is subjected to the shipping simulation according to ASTM D4169-16 DC-2, including but not limited to drop and vibration tests.

Table 6 Description of Environmental Test Conditions

Environmental test condition	Description
Cool temperature	The combination product is tested in the cool temperature of 5 ± 3°C.
Standard (room) temperature	The combination product is tested in the standard temperature of 23 ± 5°C and relative humidity of 50 ± 25% RH.
Warm temperature	The combination product is tested in the warm temperature of 40 ± 2°C and relative humidity of 50 ± 10% RH.

RH = relative humidity

Table 7 Description of Physical Test Methods

Physical test	Description
RNS removal force	Mount the combination product in tensile tester. Use the tensile tester to pull RNS off from the device and record the maximum force.
Dose accuracy	Inject the drug from combination product into a beaker that is placed on a scale. Measure the weight of the dispensed liquid and calculate the volume.
Break loose force	Mount the combination product in tensile tester. Apply force to the plunger rod until the plunger stopper initiates movement. Record the peak force.
Glide force	Mount the combination product in tensile tester. Apply force to the plunger rod and continue to push the plunger rod until its end of stroke. Record the peak glide force.
Safety System Override Force (SSORF) in compression	While in safe mode, mount the combination product in tensile tester. Apply force to the plunger rod until the safety system is overridden.
Lockout confirmation	Apply force to the plunger rod and continue to push the plunger rod until needle guard activates. Visually inspect the device to confirm lockout.
Needle access in safe mode	While in safe mode, apply a 6 mm radius sphere to the distal end of the combination product. The sphere shall not touch the needle.

RNS = rigid needle shield

Table 5-1: Acceptance Criteria Summary Table

Test Description	Test End Point	Acceptance Criteria	Sample Size	Result
Lockout Confirmation	Safety feature ready to activate after injection	(b) (4)	299	Pass: 0 failures

Table 8 **Summary of General Performance Testing after Transport Simulation; T=0**

Line #	Physical Test	Requirement	Sample Size [a]	MAX	MIN	AVE	Standard Deviation	Result (Pass/Fail)
4	Dose accuracy	(b) (4)	60	1.9937 mL	1.9639 mL	1.9791 mL	0.0047 mL	Pass
5	Lockout confirmation		59	NA	NA	NA	NA	Pass
6	Safety System Override Force in compression		29	172 N	165 N	169 N	1 N	Pass

Reviewer Comments:
- The testing and results provided (b) (4) in the MAF (b) (4) appear reasonable. There were no deviations noted. However, the sponsor didn't test activation force on the combination product. See IR#1. Resolved

4.2. Validation

In the sponsor's IR Response, they clarified that they leveraged clinical APFS stability data to demonstrate that the product maintains the EPRs to the proposed expiration date. They provided the following justification:

1. *These data will be utilized to support maintenance of EDFs over the commercial product's shelf life since the PFS-SA components remain unchanged between the clinical and commercial product. Notably, the EDFs of the APFS are characteristics of the PFS-SA: deliverable volume depends on syringe fill/finish process (fill volume), while breakloose / glide forces are driven by the syringe inner diameter, stopper friction, drug product viscosity and needle length and diameter.*

2. *The clinical and commercial presentations of the tezepelumab APFS have been verified against the same EDF specifications (see Section R.10.1). Design verification testing of the commercial combination product confirms that the EDFs are not impacted by the change in NSD design or change in the manufacturing sites, and that the commercial presentation meets the same functional requirements as the clinical presentation of the combination product.*

   Commercial design verification testing was conducted on product that was manufactured to the commercial design specification and produced using production equivalent equipment, processes, process parameters, and specifications. Similarly, clinical design verification testing was conducted on clinical product produced from the same manufacturing line that produced the clinical lots being tested on stability. By verifying each presentation with product from their respective manufacturing processes against the same performance specifications, the Sponsor established that the differences in the NSD design and manufacturing process / sites do not impact the commercial product's ability to meet the same EDF specifications as the clinical product being tested on stability.

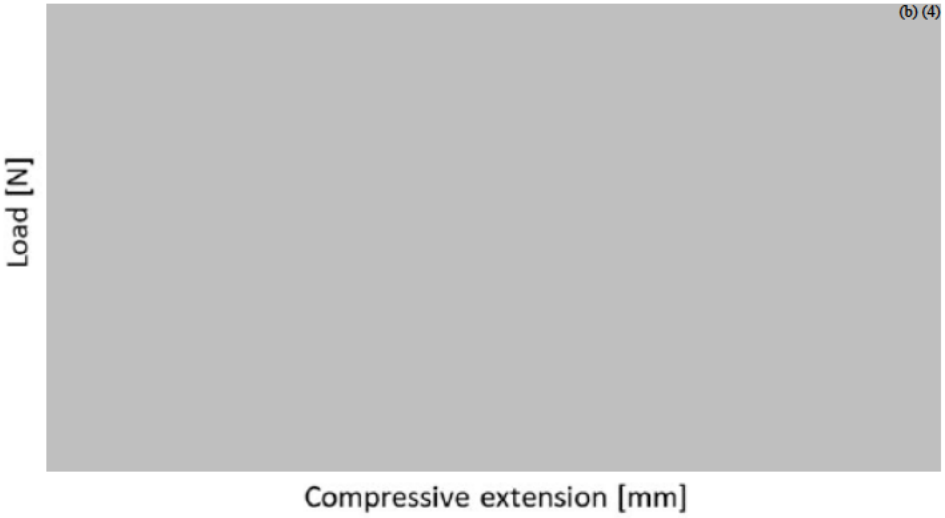
3. *To ensure that the commercial NSD activation force does not surpass the Tezepelumab glide force requirement over the shelf life of the product, results from the (b) (4) NSD aging study are provided. These data confirm that the*

commercial NSD functional performance, including activation force, continues to meet its requirements after aging through the proposed expiry.

(b) (4) conducted functional testing after accelerated aging for the commercial NSD design (b) (4) (b) (4) to support a shelf life of (b) (4) year (b) (4) The functional testing completed (b) (4) on the NSD after aging was executed against the same functional requirements as the NSD design utilized in the clinical presentation of the Sponsor's combination product. The shelf life testing of the commercial NSD included NSD activation force and was conducted with the same (b) (4) 2.25 mL syringe utilized in both the clinical and commercial presentations of the combination product. Components utilized in (b) (4) aging study meet the same design specifications the tezepelumab commercial combination product. Table 11 shows the NSD activation force tested (b) (4) after 5 years equivalent accelerating aging.

The NSD activation force requirement tested (b) (4) ((b) (4) N) is well below the combination product glide force requirement ((b) (4) N). The combination product glide force requirement accounts for the supplier's NSD activation force requirement given that the glide force includes complete depression of the plunger rod, which activates the NSD. The clinical stability data demonstrates that the PFS-SA achieves the glide force requirement after aging and the (b) (4) aging study demonstrates that the commercial NSD design continues to meet its activation force requirement after aging. Successful lockout of the NSD is both a combination product requirement and requirement tested after aging of the commercial NSD.

Figure 1 Average Break loose / Glide Force Profile for APFS with NSD Activation Force Peak at t=0, post-transport



This is a representative force profile graph by averaging 29 samples tested during t=0, post-shipping design verification test. The max NSD activation force peak was 20.2 N.

Sent the following IR to AZ on Oct 4, 2021. Received response on Oct 7, 2021:

"You are leveraging the clinical APFS break loose and glide force stability data; however, we cannot locate your full verification results. Provide the full results for the break loose and glide force verification testing on drug product that is aged (b) (4) The testing should be performed with a sample size that supports a 95% confidence and 95%

reliability. If these data were provided, please provide the location and sequence number."

Response from AZ:

The clinical accessorized prefilled syringe (APFS) break loose and glide force stability data presented in the BLA includes samples that were aged [redacted] (b) (4) (36 months) stored at 5° C. Refer to Section 3.2.P.8.3, Stability Data - Clinical [APFS] of Module 3, submitted in Seq. 0025. The clinical APFS stability data was not part of AstraZeneca's formal design verification testing plan, however, stability testing was performed using the same validated test methods as design verification testing for break loose and glide force. There are no differences in the clinical and commercial APFS that have an impact on the break loose and glide force of the APFS given that break loose and glide force is driven by the prefilled syringe subassembly (PFS-SA). Therefore, the clinical APFS stability break loose and glide force data [redacted] (b) (4) is representative of the commercial APFS performance [redacted] (b) (4)

AstraZeneca has analysed the clinical APFS stability data at 36 months per the FDA requested reliability and confidence levels as shown in Table 1. The maximum break loose and glide force measured were 12.6 N and 16.2 N, respectively, which are well below the upper specification of [redacted] (b) (4) N. The calculated k values and tolerance intervals support 95% confidence and 95% reliability with an acceptance criterion of $k_{actual} > 2.91$ per Table B.1 of ISO 11608-1:2014. Therefore, the clinical APFS stability data support the break loose and glide force requirements of the APFS being maintained [redacted] (b) (4) [redacted]

Table 1 Clinical APFS Stability Results for Break Loose and Glide Force [redacted] (b) (4) [redacted] (b) (4)

Acceptance Criteria	Test Parameter	Sample size	Time Points (months)	Max. Force (N)	Actual k Value	Test Outcome (Pass or Fail)
[redacted] (b) (4)	Peak Break Loose Force	10	36	12.6	12.94	Pass
	Peak Extrusion (Glide) Force	10	36	16.2	10.97	Pass

APFS = accessorized prefilled syringe

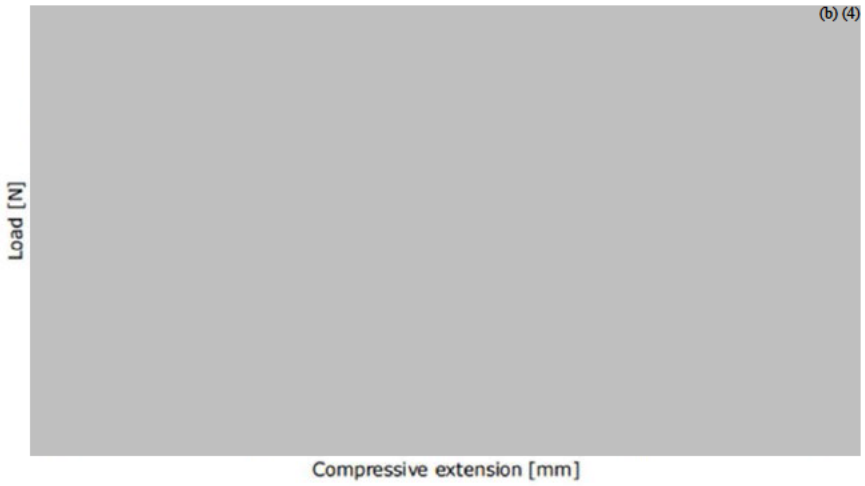
The Sponsor also conducted break loose and glide force design verification testing on the tezepelumab drug product prefilled syringe subassembly (PFS-SA) (b) (4) (b) (4) The PFS-SA samples that were tested are representative of the PFS-SA used for the commercial APFS. Design verification testing of the PFS-SA was executed using a sample size of 40 that supports 95% confidence and 95% reliability with an acceptance criterion of $k_{actual} \geq 2.13$ per Table B.1 of ISO 11608-1:2014. The 37-month results are presented in Table 2.

Table 2 PFS-SA Verification Results for Break Loose and Glide Force (b) (4) (b) (4)

Requirement	Test Parameter	Sample Size	Time Points (months)	Max. Force (N)	Actual k Value	Test Outcome (Pass or Fail)
The PFS-SA, when stored at 2-8°C (b) (4) of up to and including (b) (4) months where requirements of break loose and glide force of (b) (4) N shall be met (b) (4)	Peak Break loose Force	40	37	6.56	19.35	Pass
	Peak Extrusion (Glide) Force	40	37	14.67	2.27	Pass

PFS-SA = prefilled syringe subassembly

Figure 2 Break loose / Glide Force Curves for PFS-SA without NSD at t=0



Each curve represents the injection force profile of an individual sample.

The sponsor could not provide the EPRs for the final, finished and aged device with the NSD attached as the aging testing is currently ongoing. To demonstrate that the Glide Force (and NSD Activation Force) on the final product remains unchanged after aging, the sponsor leveraged the following data:

Table 10 Data Sources [redacted] T = 36 months

Data Source	Description	Data	Presentation	PFS-SA Configuration
Data Source #1 Stability study on 4 clinical APFS lots	Functional stability testing conducted on clinical combination product configuration with the [redacted] NSD design. Refer to Section 3.2.P.8.3, Stability Data for available stability data.	Deliverable Volume (EDF) Breakloose / Glide Force (EDF)	Clinical APFS	[redacted] 27G needle
Data Source #2 Design Verification on commercial APFS	Design Verification testing conducted on the commercial combination product [redacted] NSD design. Refer to Table 8 for T0 results.	Deliverable Volume (EDF) Breakloose / Glide Force (EDF)	Commercial APFS	[redacted] 27G needle
Data Source #3 NSD aging study [redacted]	Functional testing on commercial [redacted] NSD conducted [redacted] after accelerated aging with commercial APFS components Refer to Table 11 and DMF [redacted] for results. Letter of Authorization provided in Module 1.	NSD Activation Force [a]	Commercial NSD with commercial APFS components	[redacted] 27G needle

EDF = essential device function; NSD = needle safety device; [redacted]

[a] NSD activation force is not an EDF. However, it is important to verify that NSD design change does not impact the commercial product's ability to meet the same EDF specifications as the clinical product being tested on stability.

Table 8 Summary of General Performance Testing after Transport Simulation; T=0

Line #	Physical Test	Requirement	Sample Size [a]	MAX	MIN	AVE	Standard Deviation	Result (Pass/Fail)
1	Break loose force	The maximum break loose force shall be ≤ [redacted] N when tested at [redacted] mm/min.	29	9.2 N	5.8 N	6.7 N	1.0 N	Pass
2	Glide force	The maximum glide force shall be [redacted] N when tested at [redacted] mm/min.	29	16.1 N	10.6 N	12.7 N	1.7 N	Pass
3	RNS removal force	The RNS removal force shall be between [redacted] N.	59	29 N	15 N	18.6 N	3.0 N	Pass

Line #	Physical Test	Requirement	Sample Size [a]	MAX	MIN	AVE	Standard Deviation	Result (Pass/Fail)
4	Dose accuracy	The Drug Delivery System shall meet the dose accuracy requirement of 1.91 mL minimum when used in the standard temperature of 23 ± 5°C and relative humidity of 50 ± 25% RH.	60	1.9937 mL	1.9639 mL	1.9791 mL	0.0047 mL	Pass
5	Lockout confirmation	The Drug Delivery System needle safety feature shall lockout after the dose is delivered.	59	NA	NA	NA	NA	Pass
6	Safety System Override Force in compression	The Drug Delivery System in safe mode shall remain in safe mode, without exposure of the syringe needle, when a compressive force of up to and including (b) (4) N is applied along the same axis as the syringe needle and plunger rod.	29	172 N	165 N	169 N	1 N	Pass

Table 11 (b) (4) **NSD Activation Force after 5 Years Equivalent Accelerating Aging**

Requirement	Mean (N)	Standard Deviation (N)	Minimum (N)	Maximum (N)
NSD Activation Force (b) (4) N	5.73	1.12	3.52	8.28

NSD = needle safety device

In 3.2.P.8.3, the sponsor provided the clinical APFS (without NSD) glide force stability data for 4 lots. The stability data is for samples stored at 5°C ranges from 24-36 months and 25°C 55-65% RH from 1-3 months. Below are two lots from each temperature:

Table 1. Stability Data for Tezepelumab APFS Drug Product Supporting Lot 58918.3 Stored at 5°C

Test Method and Parameter	Acceptance Criteria	Time Point					
		T = 0	3 MO	6 MO	12 MO	24 MO	36 MO
Deliverable Volume	(b) (4)	1.96	1.94	1.94	1.94	1.93	1.93
Breakloose Force		11	11	11	11	13	13
Glide Force		18	12	13	15	15	16

Note: Glide Force is equivalent to Extrusion Force
MO = Month; N = Newtons;

Table 2. Stability Data for Tezepelumab APFS Drug Product Supporting Lot 58918.7 Stored at 5°C

Test Method and Parameter	Acceptance Criteria	Time Point				
		T = 0	3 MO	6 MO	12 MO	24 MO
Deliverable Volume	(b) (4)	1.97	1.95	1.96	1.96	1.95
Breakloose Force		9	9	8	9	9
Glide Force		10	11	10	11	12

Note: Glide Force is equivalent to Extrusion Force
MO = Month; N = Newtons;

Table 5. Stability Data for Tezepelumab APFS Drug Product Supporting Lot 58918.3 Stored at 25°C / 55 – 65% Relative Humidity

Test Method and Parameter	Acceptance Criteria	Time Point		
		T = 0	1 MO	3 MO
Deliverable Volume	(b) (4)	1.96	1.95	1.94
Breakloose Force		11	10	11
Glide Force		18	12	15

Note: Glide Force is equivalent to Extrusion Force
MO = Month; N = Newtons;

Table 6. Stability Data for Tezepelumab APFS Drug Product Supporting Lot 58918.7 Stored at 25°C / 55 – 65% Relative Humidity

Test Method and Parameter	Acceptance Criteria	Time Point	
		T = 0	3 MO
Deliverable Volume	(b) (4)	1.97	1.94
Breakloose Force		9	9
Glide Force		10	14

Note: Glide Force is equivalent to Extrusion Force
MO = Month; N = Newtons;

The data below does not include the post-approval stability study which went up to 36 months.

Figure 88. Maximum Glide Force of APFS Stored at 5°C

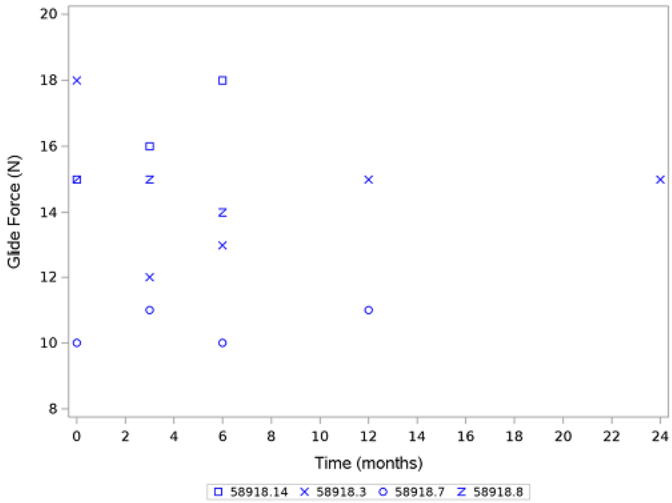
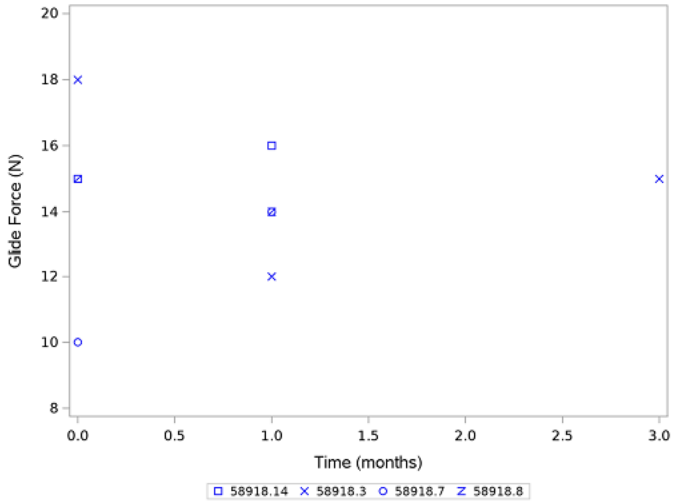


Figure 105. Maximum Glide Force for APFS Lots Stored at 25°C



Reviewer Comments:
- The manufacturer provided stability data for the NSD but the sponsor didn't provide activation force verification testing for the combination product. Since activation force is affected by glide force, we requested that the sponsor provide activation force testing on the final combination product. The sponsor cannot provide aging of the final product since the aging is ongoing. Instead, they leverage the aged clinical APFS lots, commercial APFS lots w/ NSD at t=0 and aged NSD alone. This is sufficient to demonstrate that glide force at t=0 and t=36 months remains relatively unchanged. Resolved (see above)
- Of note, they do not state how many samples are included in each lot for the clinical APFS stability testing.
- Figure 1 demonstrates that the activation force at t=0 remains below the break loose and glide force requirement of (b) (4) N. The max NSD activation force peak captured was 20.2 N. Figure 2 demonstrates that the inclusion of the NSD has a minimal impact on the injection force profile. In both Figure 1 & 2, the force profile remains below the break loose and glide force requirement of (b) (4) N. This is sufficient.
- Since the sponsor provided attribute testing on the final, finished aged & shipped product in addition to justification for leveraging clinical stability data, this appears sufficient. Their justification for leveraging data appears reasonable.

Information Request #1	(b) (4)
Sponsor Response	

(b) (4)

	(b) (4)
Reviewer Comments	1. The sponsor provided results from NSD activation attribute testing on the final, finished product that had been aged and undergone shipping testing per 95% confidence, 99% reliability as requested. Testing was performed by 6 operators (both male and female) for manual testing. All 299 samples met the acceptance criteria and passed the test. They also provided their bridging strategy to leverage the clinical APFS stability data and NSD activation graphs with real-time aging studies. They provided the Safety System Override Force shipping testing on their final, finished product using the

	commercial packaging. This is sufficient to demonstrate the verification and stability testing on the final finished product meets the specifications. 2. The sponsor provided their EPR testing after transport and demonstrated that their NSD Override Force is above their specification of (b) (4) N. This is sufficient.
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

5. 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)
Needle safety activation	Incoming acceptance and component lot release testing	Y

Reviewer Comments - The sponsor did not provide the control strategy for the Needle Safety Activation Force. See IR#1.2 Resolved

Information Request #1	(b) (4)
Sponsor Response	

	(b) (4)
Reviewer Comments	3. The sponsor clarified that the control strategy includes incoming acceptance and release testing. This is sufficient.
Response Adequate:	☑ **Yes** ☐ **No, See IR #**

<<END OF REVIEW>>

6. APPENDIX A (INFORMATION REQUESTS)

6.1. 74 Day Letter

Information Request #1

6.2. Midcycle/DRL Deficiencies

6.3. Information Requests (Post-Midcycle/DRL)