CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215866Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 215866

MOUNJARO (Tirzepatide) Injection

OPQ Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	MOUNJARO (tirzepatide) injection
Strength	2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/mL, 12.5 mg/mL, and 15 mg/mL in a pre-filled single-dose pen injector.
Route of Administration	Subcutaneous
Indication	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.
Rx/OTC Dispensed	Rx
Applicant	Eli Lilly and Company
Submissions (s) Reviewed	NDA 215866 and all submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Joseph Leginus	OPQ/ONDP/DNDAPI/NDB3
Drug Product, Labeling, and Environmental Assessment	Rao Kambhampati	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Carl Lee	OPQ/OPMA/DPMAIV/PMB12
Biopharmaceutics	N/A	N/A
Microbiology	Aditi Das	OPQ/OPMA/DMAI/MAB2
Regulatory Business Process Manager	Nowrin Kakon	OPQ/OPRO/DRBPMI/RBPMB2
Application Technical Lead	Theodore Carver	OPQ/ONDP/DNDPIII/NDPB5

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Office of Pharmaceutical Quality Review team has assessed NDA 215866 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports to have. As such, OPQ recommends approval of this NDA from a quality perspective.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Quality Assessment Summary

A. Background: The Applicant, Eli Lilly and Company, seeks U.S. marketing approval for MOUNJARO (tirzepatide) under the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetics Act. The submission relies on clinical studies, including Phase 2 and Phase 3 clinical studies, to support the safety and efficacy of tirzepatide for treatment of patients with Type 2 diabetes mellitus. Tirzepatide is a linear 39-amino acid peptide that is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with Type 2 diabetes mellitus. Tirzepatide is designed to be administered once weekly using a single-dose pen injector system, available in six different strengths (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg) in a 0.5 mL solution. NDA 215866 was accepted for priority review, and this integrated quality assessment includes reviews of the drug substance, drug product, manufacturing and facilities, and microbiology information for tirzepatide for injection.

B. Drug Substance (Tirzepatide)**:** Dr. Joseph Leginus reviewed the drug substance information and found it to be adequate. Tirzepatide is a linear 39-amino acid synthetic peptide containing two non-proteinogenic amino acids (aminoisobutyric acid or Aib) at positions 2 and 13. At the Lys-20 residue, a linear sidechain consisting of a γ-Glu linker with two 8-amino-3,6-dioxaoctanoic acids and 1,20 eicosanedioic acid is attached. The tirzepatide manufacturing process uses (b) (4) Tirzepatide was structurally characterized using a variety of methods including liquid chromatography with mass spectrometry (LC-MS), tandem mass spectrometry (LC-MS/MS) and LC-MS peptide mapping analysis, and circular dichroism (CD) spectroscopy. Dr. Leginus reviewed (b) (4) and found it to be adequate, including appropriate (b) (4) critical steps and acceptable justifications for starting materials. The release and stability specification

include appropriate analytical procedures for confirming the quality of the drug substance, including RP-LC-UV, peptide mapping, and bioassays to confirm its identity; reversed-phase HPLC for assay and impurities; size-exclusion chromatography for high molecular weight impurities; and tests for residual solvents, water content, and microbiological quality. A retest date of (b)(4) months is granted for the tirzepatide drug substance (b) (4)

C. Drug Product (Tirzepatide Injection): Dr. Rao Kambhampati reviewed the drug product information and found it to be adequate. The drug product consists of a single dose pen containing a semi-finished syringe (SFS) and an autoinjector. The drug product is manufactured in six strengths: 2.5 mg/0.5 mL, 5 mg/0.5 mL, 7.5 mg/0.5 mL, 10 mg/0.5 mL, 12.5 mg/0.5 mL. The Applicant conducted adequate formulation development and product design studies. In addition to the tirzepatide drug substance, the formulation contains the following compendial excipients: dibasic sodium phosphate heptahydrate (b) (4) sodium chloride (b) (4) and hydrochloric acid and sodium hydroxide for pH adjustment as needed. Additional testing to ensure microbiological quality were performed for dibasic sodium phosphate and sodium chloride. Overfill of the solution in the semi-finished syringe complies with USP <1151>. The drug product specification includes appropriate tests to ensure the quality of the drug product, including tests for identity by RP-HPLC and peptide mapping, assay, and impurities by RP-HPLC, high molecular weight impurities by size-exclusion chromatography, color, clarity, pH, osmolality, particulate matter, syringe functionality, sterility, and endotoxins. The limits for impurities in the proposed release and shelf-life specifications are appropriately justified and were found to be acceptable, in consultation with the nonclinical review team.
The injection solution is packaged in a (b) (4) glass syringe barrel with (b) (4) Adequate information was provided for the container closure components. Results of extractable and leachable studies confirmed the safety and compatibility of the selected (b) (4) syringe container closure systems for use in the tirzepatide injection products. See the CDRH review for assessment of the autoinjector device.

C.1. Manufacturing: Dr. Carl Lee conducted the review of the NDA with respect to the drug product manufacturing process and controls and determined that this information is adequate to support the NDA. The manufacturing process involves (b) (4) Dr. Lee evaluated the manufacturing process with respect to drug product attributes and risk to drug product quality, including (b) (4) and found that these risks to product quality are adequately controlled in the commercial manufacturing process. Evaluation of extractables studies for drug product contact equipment in consultation with the nonclinical review team indicated that levels of observed extractables are below the safety concern threshold. Overall, the process and controls were found to be adequate for the commercial manufacturing process.
Six submission batches were manufactured at Eli Lilly and Co.(Indianapolis, IN, USA); Two (2) of the 6 submission batches were manufactured at (b) (4) scale for the lowest and highest strengths. Phase 3 and primary stability batches were manufactured at Eli Lilly. The Applicant proposes commercial batch sizes of (b) (4) with equipment having the same design and operating

principles for both commercial and exhibit batches, and [redacted]. The manufacturing process for the semi-finished syringe was transferred from Eli Lilly to [redacted] through technology transfer. [redacted] manufactured 2 batches at the [redacted] commercial scale, using the same process developed at Eli Lilly. One batch was manufactured at [redacted] for 2.5mg/0.5ml and one batch at [redacted] for 15mg/0.5ml. [redacted]. Results of comparative studies support the technology transfer between the two sites. Assembly of the autoinjector device including the SFS is performed at Eli Lilly and Co. (Indianapolis, IN, USA).

C.2. Microbiological Aspects: Dr. Aditi Das conducted the microbiology review and concluded that the information to support microbiological quality is adequate. Dr. Das reviewed the manufacturing process [redacted] to ensure microbiological quality, including bioburden reduction, and found them to be adequate. The description of the environmental monitoring program is acceptable. The Applicant provided acceptable validation studies [redacted]. The applicant provided an acceptable description of the container closure integrity test (CCIT) and adequate data following CCIT validation studies. The analytical procedures and acceptance criteria for endotoxins and sterility in the drug product specification are acceptable.

C.3. Biopharmaceutics Aspects: Since the drug product is an injectable solution, a biopharmaceutics review is not applicable for this submission.

III. Stability, Storage Conditions and Expiration Date

Dr. Rao Kambhampati reviewed the long-term stability studies and other studies for the drug product supporting the storage conditions. The Applicant provided 18 months of real-time long-term stability data (5°C) and 6 months accelerated stability data at (30°C/65%RH) for three registration batches of the highest and lowest strengths. In addition, the Applicant provided 30 months supportive data for two clinical batches and statistical analyses of the stability data. During review of the stability data, issues related to data variability and limits for impurities were resolved. In addition to the long-term stability data, the Applicant provided 30 days of in-use stability data at 30°C [redacted] For review of stability of the injection device, see the CDRH review.

An expiration dating period of 24 months is granted for all strengths of tirzepatide injection, when the drug product is stored in refrigerator at 2°C to 8°C (36°F - 46°F) and protected from light. An [redacted] storage period of 21 days is granted for the drug product stored at temperatures below 30°C and protected from light.

IV. Quality Labeling

Dr. Rao Kambhampati reviewed the product quality aspects of the product labeling. The prescribing information is adequate. Addition of storage conditions to the medication guide is proposed.

Addition of active and inactive ingredient information and storage conditions are proposed for the container label on the pen injector. The labeling will be deemed adequate when these revisions to the labeling are addressed.

V. Assessment of Manufacturing Facilities

Dr. Carl Lee conducted the review of the manufacturing facilities. Dr. Lee's overall facility assessment recommendation is approval based on the previous history for each manufacturing facility, with no deficiencies noted for any facility. Drug substance manufacturing is performed at (b) (4) The drug product is manufactured at either Eli Lilly and Co. (Indianapolis, IN; FEI: 1819470) (b) (4) Final device assembly is performed at either Eli Lilly and Co. (Indianapolis, IN; FEI: 1819470) or Eli Lilly Italia SPA (Sesto Fiorentino, FI, Italy; FEI: 3002806895). Several drug product test sites are also included in the NDA. For a tabulated listing of all sites, manufacturing responsibilities, and status at time of review, see the Facilities table on p. 2 of the manufacturing assessment.

VI. Environmental Assessment

The Applicant requested a claim of categorical exclusion from the requirement for an environmental assessment (EA), pursuant to 21 CFR 314.50 (d), based on the exclusion allowed by 21 CFR 25.31 (b) and (c). This claim is granted, because the projected annual sales of tirzepatide would result in far less than 1 ppb of tirzepatide at the point of entry into the aquatic environment, concentrations that are excluded from an EA under 21 CFR 24.31(b). (b) (4) The Applicant knows of no extraordinary circumstances that would require an environmental assessment.

VII. Life Cycle Knowledge Information

Final Risk Assessment for NDA 215866

Attribute/ CQA	Factors Impacting CQAs	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations
Assay, Purity, Stability	• Formulation Container closure • Raw materials • Process parameters • Scale/ equipment/ • site	Medium	(b) (4)	Acceptable	N/A
Dose Accuracy	• Formulation • Container closure and injection device • Raw materials	Low		Acceptable	N/A; see CDRH review.
Sterility	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	High		Acceptable	N/A
Endotoxin Pyrogen	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment Site	Medium		Acceptable	N/A
Related Substances	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Acceptable	N/A

			(b) (4)		
pH	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Acceptable	N/A
Osmolality	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Acceptable	N/A
Extractables/ Leachables	• Formulation • Container/closure • Process parameters • Scale/equipment • Site	Medium		Acceptable	N/A
Particulate Matter	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment Site	Low		Acceptable	N/A

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

At present, there are no outstanding deficiencies related to the drug substance, drug product, microbiology, manufacturing, and environmental assessment sections of this NDA. The OPQ overall recommendation for NDA 215866 is approval.

Theodore Carver, Ph.D.
Senior Product Quality Assessor, OPQ/ONDP/DNDPIII/NDPB5

CHAPTER IV: LABELING
NDA 215866

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The proposed Prescribing Information (PI) is adequate.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION (PI)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	MOUNJARO (tirzepatide) injection
Route(s) of administration	Adequate	Subcutaneous use
Dosage Forms and Strengths Heading in Highlight		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	• Injection: 2.5 mg/0.5 mL single-dose pen • Injection: 5 mg/0.5 mL single-dose pen • Injection: 7.5 mg/0.5 mL single-dose pen • Injection: 10 mg/0.5 mL single-dose pen • Injection: 12.5 mg/0.5 mL single-dose pen • Injection: 15 mg/0.5 mL single-dose pen
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	Single-dose pen
If the drug product contains an active ingredient that is a salt, clearly state whether the strength	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

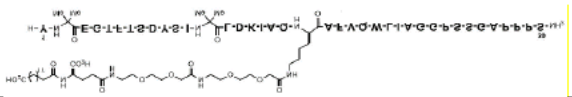
Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	Inspect MOUNJARO visually before use. It should appear clear and colorless to slightly yellow. Do not use MOUNJARO if particulate matter or discoloration is seen.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to	N/A	

another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Injection
Strength(s) in metric system	Adequate	• Injection: 2.5 mg/0.5 mL single-dose pen • Injection: 5 mg/0.5 mL single-dose pen • Injection: 7.5 mg/0.5 mL single-dose pen • Injection: 10 mg/0.5 mL single-dose pen • Injection: 12.5 mg/0.5 mL single-dose pen • Injection: 15 mg/0.5 mL single-dose pen
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Clear, colorless to slightly yellow solution available in pre-filled single-dose pens.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-dose

Section 11 (DESCRIPTION)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	MOUNJARO (tirzepatide) injection
Dosage form(s) and route(s) of administration	Adequate	Injection, for subcutaneous use
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may be added to adjust the pH.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	Sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may be added to adjust the pH.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	MOUNJARO is a clear, colorless to slightly yellow, sterile, preservative-free solution for subcutaneous use.
Pharmacological/Therapeutic class	Adequate	Dual GIP and GLP-1 receptor agonist
Chemical name, structural formula, molecular weight	Adequate	It is a 39-amino acid peptide. (b) (6) GIP sequence containing 2 non-coded amino acids (aminoisobutyric acid, Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 is attached to 1,20-eicosanedioic acid via a linker. The molecular weight is 4813 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$. 
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	MOUNJARO has a pH of 6.5 – 7.5.

Section 11 (DESCRIPTION) Continued

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	MOUNJARO is a clear, colorless to slightly yellow solution available in pre-filled single-dose pens.
Strength(s) in metric system	Adequate	2.5 mg/0.5 mL solution 5 mg/0.5 mL solution 7.5 mg/0.5 mL solution 10 mg/0.5 mL solution 12.5 mg/0.5 mL solution 15 mg/0.5 mL solution
Available units (e.g., bottles of 100 tablets)	Adequate	Carton of 4 Single-Dose Pens
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	MOUNJARO is a clear, colorless to slightly yellow solution available in pre-filled single-dose pens. Each pen contains 0.5 mL of solution. • 2.5 mg/0.5 mL solution, NDC 0002-1506-80 • 5 mg/0.5 mL solution, NDC 0002-1495-80 • 7.5 mg/0.5 mL solution, NDC 0002-1484-80 • 10 mg/0.5 mL solution, NDC 0002-1471-80 • 12.5 mg/0.5 mL solution, NDC 0002-1460-80 • 15 mg/0.5 mL solution, NDC 0002-1457-80
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Single-dose pens

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	• Store MOUNJARO in a refrigerator at 36°F to 46°F (2°C to 8°C). • If needed, each single-dose pen can be stored unrefrigerated at temperatures not to exceed 86ºF (30ºC) for up to 21 days. • Do not freeze MOUNJARO. Do not use MOUNJARO if frozen. • Store MOUNJARO in the original carton to protect from light.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	• Store MOUNJARO in a refrigerator at 36°F to 46°F (2°C to 8°C). • If needed, each single-dose pen can be stored unrefrigerated at temperatures not to exceed 86ºF (30ºC) for up to 21 days.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling: Not applicable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items Proposed in PI Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments on PI Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

2.0 PATIENT LABELING:

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides): Medication Guide is assessed below

Item	Items Proposed in Medication Guide (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Medication Guide (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	MOUNJARO™ (mown-JAHR-OH) (tirzepatide) injection, for subcutaneous use
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Inadequate	Include storage and handling information.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	tirzepatide
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Sodium chloride, sodium phosphate dibasic heptahydrate, hydrochloric acid solution, sodium hydroxide solution, in water for injection
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Marketed by Lilly USA, LLC Indianapolis, IN 46285, USA

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

Drug product is supplied in six different strengths as indicated below:

- Injection: 2.5 mg/0.5 mL single-dose pen
- Injection: 5 mg/0.5 mL single-dose pen
- Injection: 7.5 mg/0.5 mL single-dose pen
- Injection: 10 mg/0.5 mL single-dose pen
- Injection: 12.5 mg/0.5 mL single-dose pen
- Injection: 15 mg/0.5 mL single-dose pen

A representative example of the proposed container label on the 15 mg/0.5 mL single-dose prefilled pen is provided below:

Item	Items Proposed in Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	Mounzaro™ (tirzepatide) injection
Strength(s) in metric system	Adequate	15 mg/0.5 mL
Route(s) of administration	Adequate	Subcutaneous use only
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	0.5 mL
"Rx only" displayed on the principal display	Adequate	Rx only
NDC	Adequate	NDC 0002-1457- (b) (4)
Lot number and expiration date	Adequate	Yes, space was included for lot number and expiration date printing.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	Storage conditions were not included on the prefilled pen label probably because the label is small and the pen should be stored in the original carton, which contains storage conditions.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	Single-Dose Pen
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	Active and inactive ingredient information was not included on the prefilled pen label probably because the label is small.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Included

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items Proposed in Container Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Container Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Marketed by Lilly USA, LLC Indianapolis, IN 46285 USA
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others if space is available.	N/A	

3.2 Carton Labeling:

A representative example of the carton label proposed for packaging of 4 x 15 mg/0.5 mL single-dose prefilled pens is provided below:

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

Item	Items Proposed in Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[4], (font size and prominence)	Adequate	Mounjaro™ (tirzepatide) injection
Strength(s) in metric system	Adequate	15 mg/0.5 mL
Route(s) of administration	Adequate	For subcutaneous use only
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	4 single-dose prefilled pens. 4 x 15 mg/0.5 mL prefilled pens.
"Rx only" displayed on the principal display	Adequate	Rx Only
NDC	Adequate	NDC 0002-1457-80
Lot number and expiration date	Adequate	Space included for printing lot number and expiration date
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store refrigerated at 36°F to 46°F [2°C to 8°C] in original carton to protect from light. Do not freeze. Mounjaro can be stored at room temperature up to 86°F (30°C) for up to 21 days in the carton. (b) (4) Discard if not used within 21 days after removing from the refrigerator.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	Single-dose pen
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	Each 0.5 mL of Mounjaro contains 15 mg tirzepatide; sodium chloride (4.1 mg), sodium phosphate dibasic heptahydate (0.7 mg), and water for injection. Hydrochloric acid and/or sodium hydroxide solution may be added to adjust the pH.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Included

Item	Items Proposed in Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Marketed by: Lilly USA, LLC Indianapolis, IN 46285 USA
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Carton contains: 4-Single-dose prefilled pens, Package insert, Medication Guide Instructions for Use.
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Container and Carton Labeling: The carton labeling is adequate. The container (prefilled dosing pen) label will be adequate if the following suggested changes are incorporated in the revised documents.

Overall Assessment and Recommendation: Adequate with the following proposed changes:

1) **In the medication guide, include storage and handling information.**
2) **On the prefilled dosing pen label, include active and inactive ingredient information and storage conditions**

Primary Labeling Assessor Name and Date: Rao V Kambhampati, Ph.D. 1/31/2022

[4] Established name = [Drug] [Route of Administration] [Dosage Form]

Rao Kambhampati

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Mohan Sapru

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U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	Indicated for Treatment of Type 2 Diabetes
NDA Number	215866
Assessment Cycle Number	1
Drug Product Name / Strength	MOUNJARO (Tirzepatide), 2.5, 5, 7.5, 10, 12.5, 15 mg/0.5mL
Route of Administration	Subcutaneous Injection
Applicant Name	Eli Lilly and Company
Manufacturing Site	Lilly Corporate Center Indianapolis, Indiana 46285 USA
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A

Assessment Summary:

- This review covers sterility assurance and microbiological quality of the drug product.
- The product is (b) (4) filled. No deficiencies were found.

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
09/14/2021	09/14/2021	N/A	09/17/2021

Theodore Carver

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/s/

THEODORE E CARVER
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