

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217806Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	4		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	217806		
Applicant Name	Eli Lilly and Company		
Drug Product Name	ZEPBOUND (tirzepatide)		
Dosage Form.	Injection		
Proposed Strength(s)	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/0.5mL, and 15 mg/0.5mL in a single dose pen injector		
Route of Administration	Subcutaneous		
Maximum Daily Dose	15 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • 30 kg/m² or greater (obesity) or • 27 kg/m² or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, (b) (4), type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease). (1)		
Drug Product Description	Each strength of tirzepatide is provided in a single dose pen injector		
Co-packaged product information	N/A		
Device information:	The device part of the drug product consists of a syringe contained in a single-use autoinjector.		
Storage Temperature/ Conditions	2°C to 8°C (36°F to 46°F)		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	N/A; see review of NDA 215866	N/A





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	<i>Drug Product/ Labeling</i>	See review of NDA 215866/ Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
	<i>Manufacturing</i>	Naresh Pavurala CDER/OPQ/OPMA/DPMAIII/ PMB8	Nallaperumal Chidambaram CDER/OPQ/OPMA/DPMAIII/ PMB8
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	Aditi Das OPQ/OPMA/DMAI/MAB2	Yuansha Chen OPQ/OPMA/DMAI/MAB2
	<i>Other (specify):</i>	N/A; see review of NDA 215866	N/A
	<i>RBPM</i>	Oluwafunmike (Funke) Ajomale OPQ/OPRO/DRBPMIII/RBPMB7	
	<i>ATL</i>	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

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.

b. Additional Comments for Action

None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1. Background

Eli Lilly and Company is seeking marketing approval of tirzepatide, with the proposed tradename ZEPBOUND™, for an additional indication, as an adjunct to a reduced-calorie diet and increased physical activity for chronic



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weight management in adults with an initial body mass index (BMI) of 30 kg/m² or greater (obesity) or 27 kg/m² or greater (overweight) in the presence of at least 1 weight-related comorbid condition (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, or type 2 diabetes mellitus). NDA 217806 was submitted as a rolling submission, with the complete NDA submission, including Modules 2.3 and 3, submitted on May 8th, 2023. Tirzepatide was previously approved under the tradename MOUNJARO™ as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) on May 13th, 2022 (NDA 215866, submitted by the same Applicant). The drug products in NDA 217806, including the six strengths of tirzepatide, are identical to the equivalent pen injector drug products approved in NDA 215866.

NDA 217806 cross-references all chemistry, manufacturing, and controls (CMC) information to NDA 215866 approved at time of submission of the CMC part of NDA 217806, including the quality amendment submitted in eCTD sequence 43, which provides for addition of a new manufacturer of the glass syringes, approved on December 20th, 2022. Therefore, no new CMC information was submitted in the original NDA 217806. A statement providing for cross-referencing of all information in Modules 2.3 and 3 to NDA 215866 is included in Module 1.4.4 of the NDA. Reviews of manufacturing to confirm adequacy of process and facilities, of microbiology to address a specific requirement for validation of analytical procedures, of quality aspects of the drug product labeling, and the claim for categorical exclusion from environmental assessment are included in this integrated quality assessment. For all other reviews of CMC information, refer to the CMC review of the relevant information for NDA 215866.

2. Manufacturing

No new manufacturing information was submitted in NDA 217806. The process and facilities information provided in NDA 215866 were reviewed and found to be adequate to support approval of NDA 217806.

3. Microbiology

Although all microbiology information is cross-referenced to NDA 215866, the microbiology review team requested that the Applicant provide additional information regarding validation studies for bacterial endotoxin testing. This information was provided by the applicant and found to be acceptable after review. Therefore, the review team recommends approval of NDA 217806 from the microbiology perspective.

4. Quality Labeling



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The quality aspects of the labeling for NDA 217806 were reviewed and found to be acceptable.

5. Environmental Analysis

The Applicant claims Categorical Exclusion from the requirement for an environmental assessment pursuant to 21 CFR 25.15(d) based on the exclusion allowed by 21 CFR 25.31(b) and (c). The Applicant provided a calculation based on peak annual sales of tirzepatide demonstrating that the maximum expected introduction concentration of tirzepatide will be less than 1 ppb at the point of introduction into the aquatic environment. In addition, the Applicant provided information to support degradation of tirzepatide into the same degradation products known to form from naturally occurring proteins and fatty acids (amino acids and acetyl CoA). The Applicant indicates that there are no known extraordinary circumstances that could require an environmental assessment. Therefore, after review of the information provided by the Applicant, a categorical exclusion from environmental assessment is granted.

6. Other CMC information

As indicated above, all other CMC information is cross-referenced to NDA 215866. Information provided for the drug substance and drug product in NDA 215866 are adequate to support approval of NDA 217806.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	N/A
Microbiology	-	Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments: None.

Comparability Protocols (PACMP): No

Comments: None.

Additional Lifecycle Comments: None.





Theodore
Carver

Digitally signed by Theodore Carver

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Title:	NDA IQA Template CHAPTER IV-LABELING
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CHAPTER IV: LABELING

NDA Number	217806
Assessment Cycle Number	1
Drug Product Name	ZEPBOUND (tirzepatide)

Assessment Recommendation: Choose an item.

Item	Assessment Conclusion	SDN # where labeling is adequate (“N/A” otherwise)
Prescribing Information Labeling	Adequate	9
Patient Information	Adequate	9
Instruction for Use (IFU)	Adequate	9
Container Labels	Adequate	9
Carton Labeling	Adequate	9

Brief Description of Outstanding Issues: None.

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
eCTD #1, SD #!	11/17/22	Container labeling
eCTD #9, SD #9	5/8/23	USPI, carton, medguide, ifu labeling

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

¹ Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(copy of proposed text)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	'ZEPBOUND™ (tirzepatide) injection'
Route(s) of administration	Adequate	'for subcutaneous use'
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen (3)
If the drug product contains an active ingredient that is a salt, clearly state whether the strength 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). ⁶	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored." ⁷	N/A	

² Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

⁴ Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

⁵ Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

⁶ Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

⁷ Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For injectable drug products for parenteral 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. ⁸	Adequate	Single-dose pen

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

(copy of proposed text)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (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 and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).	N/A	

⁸ Guidance: [Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use \(October 2018\)](#); USP <659>

⁹ See § 201.57(c)(3); draft guidance: [Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format \(January 2023\)](#); Labeling Review Tool (March 2022, page 25)

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	'Inspect ZEPBOUND visually before use. It should appear clear and colorless to slightly yellow. Do not use ZEPBOUND if particulate matter or discoloration is seen.'
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	Adequate	See above statement.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
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 <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures."</i> ^x with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

(copy of proposed text)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
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 (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	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	'Injection: 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 parenteral 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 (see USP <659>).	Adequate	

Assessment: Choose an item.

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

1.2.3 Section 11 (DESCRIPTION)¹⁴

(copy of proposed text)

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate	
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	
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)” [§ 201.57(c)(12)(i)(C)].	N/A	
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	

¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

¹⁵ Use of “USP” descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the “USP” descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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. [§ 201.100(b)(5)(iii)].	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	Adequate	
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	‘tirzepatide, a once weekly GIP receptor and GLP-1 receptor agonist’
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	‘ZEPBOUND has a pH of 6.5 – 7.5’
For oral prescription drug products, include gluten statement ¹⁹ (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	

¹⁷ Listed before “indicated for” in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term “FDA EPC Text Phrases” in [FDA’s Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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	

Assessment: Choose an item.

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)²⁰

(copy of proposed text)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	
Strength(s) in metric system. [§ 201.57(c)(17)(i)] 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. No equivalency statement.	Adequate	Active ingredient is not a salt.
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	

²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	'ZEPBOUND is a clear, colorless to slightly yellow solution available in pre-filled single-dose pens as follows:'
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 parenteral 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 (see USP <659>).	Adequate	See above
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." [§ 201.57(c)(17)(iv)]	Adequate	• Store ZEPBOUND in a refrigerator at 2°C to 8°C (36°F to 46°F). • If needed, each single-dose pen can be stored unrefrigerated at temperatures not to exceed 30°C (86°F) for up to 21 days. • Do not freeze ZEPBOUND. Do not use ZEPBOUND if frozen. • Store ZEPBOUND in the original carton to protect from light. See IQA for cross-referenced NDA 215866 for information to support storage and in-use conditions.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	
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	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
natural rubber latex, state: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."²¹</i>		
Include information about child-resistant packaging ²² (if chosen by manufacturer).	N/A	

Assessment: Choose an item.

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

²¹ Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)

²² Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose “Adequate” or “Inadequate”)	Assessor’s Comments (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

Assessment: Choose an item.

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed 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 ²⁴	Adequate	ZEPBOUND™ (ZEHP-bownd) (tirzepatide) injection, for subcutaneous use
Special preparation instructions (if applicable).	N/A	
Storage and handling information (if applicable).	Adequate	
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 differ from the dosage form.	N/A	
Active ingredient(s) (if applicable).	Adequate	tirzepatide

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

²⁴ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed 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)
Alphabetical listing of inactive ingredients (if applicable).	Adequate	Inactive ingredients: sodium chloride, sodium phosphate dibasic heptahydrate, and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH
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

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

3.0 CONTAINER AND CARTON LABELING²⁵

The drug product is supplied in six different strengths in single-dose pens: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL

3.1 Container Labels²⁶

Representative container label for 2.5 mg/0.5 mL strength:

²⁵ [Carton and Container Labeling Resources](#)

²⁶ Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.



3.2 Carton Labeling

Representative carton label for 2.5 mg/0.5 mL strength:

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	N/A
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Adequate	Yes	0.5 mL
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	No	Pen is required to be stored in the carton and insufficient space for full storage conditions on container label.

²⁷ Established name = [Drug] [Route of Administration] [Dosage Form]

²⁸ Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See [Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

²⁹ § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
For injectable drug products for parenteral 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. (See USP <659>).	Adequate	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	No	Pen is required to be stored in the carton and insufficient space ingredient list on container label.
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	Adequate	No	Pen is required to be stored in the carton and insufficient space ingredient list on container label.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	N/A
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	

³⁰ See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Choose an item.	Choose an item.	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	No	(b) (4)
No text on Ferrule and Cap overseal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	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	Yes	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. ³¹	N/A	Yes	N/A
And others if space is available.	N/A	Choose an item.	N/A

³¹ USP General Notices 3.20 Indicating Conformance

Assessment of Carton Labels and Container Labeling: *Adequate*

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

None.

Primary Labeling Assessor Name and Date:

Theodore Carver Ph.D. 9/22/23



Theodore
Carver

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Date: 10/06/2023 12:12:06AM

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MICROBIOLOGY

Product Information	Indicated for Treatment of Chronic Weight Management in Adults with Obesity, or Overweight and Weight-related Comorbidities
NDA Number	217806
Assessment Cycle Number	1
Drug Product Name / Strength	ZEPBOUND (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 is a rolling submission which cross-references the approved NDA 215866 for CMC (including microbiological issues) and this review only covers an information request (IR) on bacterial endotoxins testing of the drug product.
- No deficiencies were found.

List Submissions Being Assessed (table):

Submit	Received	Review Request	Assigned to Reviewer
11/17/2022	11/17/2022	N/A	
04/20/2023	04/20/2023	N/A	

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues: None

Supporting Documents: N215866MR01.docx (Adequate) dated 12/13/2021, BLA761063.Rev.memo.DP.052218.pdf

Select Number of Approved Comparability Protocols: 00

Review notes: NDA 217806 is submitted by the applicant, Eli Lilly and Company (Lilly) for approval of tirzepatide, with the proposed tradename ZEPBOUND™, for treatment of Chronic Weight Management (CWM) in Adults with Obesity, or Overweight and Weight-related Comorbidities. Tirzepatide development for CWM was conducted under IND 139721. The current NDA was a rolling submission, with the first sequence submitted in 11/2022, whereby the CMC portion (Modules 2 and 3) was incorporated by cross-reference to an approved NDA. The cross-referenced NDA 215866 was approved on 13 May 2022, for the same drug product and strengths, i.e., tirzepatide, under the tradename MOUNJARO™, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

From the Microbiology (CMC) perspective, an IR was conveyed on 03/23/2023 regarding bacterial endotoxins testing, and a response was received from the applicant on 04/20/2023. The current review is a memo covering only the Micro IR and IR response. For the rest of the sterility assurance and microbiological quality of the drug product assessment, please refer to NDA 215866 and micro review, N215866MR01.docx (Adequate) dated 12/13/2021.

Lilly indicates that NDA 217806 includes Module 3 content via a cross reference to approved NDA 215866. Therefore, Lilly will add these reports to NDA 215866 in the 2023 annual report.



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MICROBIOLOGY LIST OF DEFICIENCIES:

None

Primary Microbiology Assessor Name and Date:

Aditi Das, Ph.D., 9/12/2023

Secondary Assessor Name and Date:

Yuansha Chen, Ph.D., 09/12/2023



Aditi
Das

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Yuansha
Chen

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Theodore
Carver

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/s/

THEODORE E CARVER
10/06/2023 10:37:24 AM