CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761467Orig1,Orig2s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date:

1. Application/Product Information

BLA number	761467
Submission Type	Original Submission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	BLA 125514; IND 161465, IND 110080, IND 116833
Review Designation	Priority Review (via voucher)
Applicant	Merck Sharp & Dohme LLC
Indication	All adult and pediatric (12-17 years old) solid tumor indications currently approved for pembrolizumab IV BLA 125514
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Keytruda Qlex
	Non-proprietary Name/Code Name: pembrolizumab and berahyaluronidase alfa-pmph
	OBP Naming: MAB HUMANIZED (IGG4) ANTI Q15116 (PDCD1_HUMAN) [MK3475]; RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20] [MK3475A]
Drug Product Description	Keytruda Qlex is supplied as a fixed dose combination of pembrolizumab and berahyaluronidase alfa in a single-use vial as a solution for injection for subcutaneous (SC) administration. The drug product formulation is 165 mg/mL pembrolizumab and 2000 U/mL berahyaluronidase alfa in (b) (4) mg/mL (b) (4) histidine, (b) (4) mg/mL (b) (4) histidine hydrochloride monohydrate, (b) (4) mg/mL (b) (4) methionine, (b) (4) mg/mL sucrose, and (b) (4) mg/mL polysorbate 80, at a pH of 5.3-5.9.

	Pembrolizumab (MK-3475) is a humanized IgG4 kappa monoclonal antibody (mAb) that binds to the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor on T cells, thereby inhibiting T cell proliferation and cytokine production. Berahyaluronidase alfa (MK-5180), a novel variant of human hyaluronidase PH20, is included to enhance dispersion and allow SC administration of pembrolizumab.		
Dosage Form	Solution for injection		
Strength	• 790 mg pembrolizumab and 9600 units berahyaluronidase alfa/(b) (4) mL • 395 mg pembrolizumab and 4800 units berahyaluronidase alfa/(b) (4) mL		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	(b) (4) clear glass vials with (b) (4) stopper and aluminum seal with plastic flip-off cap.		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Eun Hee Koh	Anshu Rastogi
	Drug product	Kun Dong	Anshu Rastogi
	Immunogenicity Assay	Eun Hee Koh	Anshu Rastogi
	Facility	Chani Broner (DS) Bingchen Du (DP)	Zhong Li
	Microbiology	Chani Broner (DS) Bingchen Du (DP)	Denise Miller

	RBPM	Andrew Shiber
	ATL	Anshu Rastogi
OPQ Issued Consults	None	

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761467 for Keytruda Qlex manufactured by Merck Sharp & Dohme LLC. The data submitted in this application are adequate to support the conclusion that the manufacture of Keytruda Qlex is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:**
  Pembrolizumab 165 mg/mL: (b) (4)
  Berahyaluronidase alfa: (b) (4)
- **Drug Product:**
  Manufacture: BSP Pharmaceuticals S.p.A, Latina Scalo, Italy (FEI: 3007255826)
  Packaging: Merck Sharp & Dohme LLC, Wilson, North Carolina (FEI: 1036761), and Merck Sharp & Dohme B.V., Haarlem, Netherlands (FEI: 3002807658)

b. Fill size and dosage form: 2.4 mL (395 mg pembrolizumab and 4800 units berahyaluronidase alfa) and 4.8 mL (790 mg pembrolizumab and 9600 units berahyaluronidase alfa) Type (b) (4) glass vials as solution for injection for subcutaneous administration.

c. Dating Period:

- **Drug Product:** 24 months at 5 ± 3 °C
- **Drug Substance:**
  - (b) (4) months at (b) (4) °C (b) (4) for pembrolizumab 165 mg/ml
  - (b) (4) months at (b) (4) °C (b) (4) for berahyaluronidase alfa

- Intermediate Substance, if applicable: N/A
- For packaged products:
  - Component: N/A
  - Component: N/A
- Stability Option:
  - For stability protocols:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your berahyaluronidase alfa drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:
   - Yes
   - Rationale, if exempted: Keytruda Qlex is exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

Keytruda Qlex is indicated for the treatment of all adult and pediatric (12-17 years old) solid tumor indications currently approved for pembrolizumab IV under BLA 125514. Keytruda Qlex is supplied as a fixed dose combination of pembrolizumab and berahyaluronidase alfa in a single-use vial as a solution for injection for subcutaneous (SC) administration. Pembrolizumab (MK-3475) is a humanized IgG4 kappa monoclonal antibody (mAb) that binds to the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor on T cells, thereby inhibiting T cell proliferation and cytokine production. Berahyaluronidase alfa (MK-5180), a novel variant of human hyaluronidase PH20, is included to enhance dispersion and allow SC administration of pembrolizumab. The drug product is supplied as single dose vials containing 165 mg/mL pembrolizumab and 2000 U/mL berahyaluronidase alfa in (b) (4) mg/mL (b) (4) histidine, (b) (4) mg/mL (b) (4) histidine hydrochloride monohydrate, (b) (4) mg/mL (b) (4) methionine, (b) (4) mg/mL sucrose, and (b) (4) mg/mL polysorbate 80, at a pH of 5.3-5.9.

The potency of pembrolizumab is evaluated through a chemiluminescent competitive binding ELISA that evaluates the ability of pembrolizumab to compete with PD-1 ligand (PD-L1) for binding to PD-1. The method detects levels of PD-L1 bound to PD-1/Fc (PD-1) immobilized on an ELISA plate, in the presence of increasing concentrations of pembrolizumab. Luminescence is measured using a microplate reader and resulting inhibition response curves are analyzed with curve fitting software (e.g., SoftMax Pro). The EC50 values generated from this assay are a measurement of the ability of pembrolizumab

to inhibit PD-L1 binding to PD-1/Fc. Biological potency is expressed as %relative potency of pembrolizumab reference material.

Specific activity of berahyaluronidase alfa is determined using an enzyme-based microturbidity assay. Hyaluronic acid (HA) binds to albumin and the albumin-HA complex becomes turbid. When HA is hydrolyzed by hyaluronidase, the turbidity of the albumin-HA complex decreases. Therefore, this assay measures turbidity (OD values) with a plate reader to determine hyaluronidase enzymatic activity.

The (b) (4) drug substance (DS) manufacturing process for pembrolizumab 165 mg/ml is (b) (4)

The drug product (DP) is manufactured (b) (4)

The overall manufacturing control strategy incorporates controls over raw materials, facilities and equipment, manufacturing processes, adventitious agents, microbial contamination, and release and stability of the drug substances and drug product. The manufacturing processes and overall control strategies for Keytruda Qlex as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for manufacture at the (b) (4)

(b) (4) facilities proposed for pembrolizumab 165 mg/ml DS and berahyaluronidase alfa manufacture, respectively, and BSP Pharmaceuticals S.p.A, Latina Scalo, Italy (FEI: 3007255826) proposed for DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology, and sterility assurance perspectives.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for Keytruda Qlex (i.e., there is no specific test method described in regulation for Keytruda Qlex that establishes an official standard of potency). We next considered whether potency is a factor for Keytruda Qlex within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Keytruda Qlex for purposes of § 610.61(r) because lot variability is not a concern for Keytruda Qlex as Keytruda Qlex's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations
   a. Established Conditions based on ICH Q12 principles: No

   b. Drug Substance (Pembrolizumab 165 mg/mL):
      i. Protocols approved:
         1. Protocol for qualification of primary and secondary reference standards (RS program cross-referenced to BLA 125514)
         2. Pembrolizumab 165 mg/mL stability protocol

3. Protocol for new working cell bank
4. Protocol [redacted]

ii. Residual risk: None
iii. Future inspection points to consider:

c. Drug Substance (Berahyaluronidase alfa):

i. Protocols approved:
1. Protocol for qualification of primary and secondary reference standards
2. Protocol for [redacted] PRS and SRS
3. Protocol for qualification of [redacted] calibration standard
4. Berahyaluronidase alfa stability protocol
5. Berahyaluronidase alfa stability protocol for primary stability batches
6. [redacted] protocol
7. [redacted] protocol
8. [redacted] protocol
9. [redacted] protocol

ii. Residual risk: None
iii. Future inspection points to consider:

d. Drug Product:

i. Protocols approved:
1. Protocol for qualification of a new DP calibration standard
2. Pembrolizumab + Berahyaluronidase alfa stability protocol
3. Shelf life extension protocol

ii. Residual risk: None
iii. Future inspection points to consider:

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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

/s/

ANSHU RASTOGI
09/15/2025 11:51:44 AM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	August 26, 2025
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Kun Dong, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIII
Application:	BLA 761467
Applicant:	Merck Sharp & Dohme LLC US License 0002
Submission Date:	January 23, 2025
Product:	Keytruda Qlex (pembrolizumab and berahyaluronidase alfa-pmph)
Dosage form(s):	injection
Strength and Container-Closure:	395 mg pembrolizumab and 4,800 units berahyaluronidase alfa-pmph per 2.4 mL (165 mg/2,000 units per mL) solution in a single-dose vial 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa-pmph per 4.8 mL (165 mg/2,000 units per mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information and medication guide (submitted on August 25, 2025), and container labels and carton labeling (submitted on August 20, 2025) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

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

CONCLUSION

The prescribing information and medication guide (submitted on August 25, 2025), and container labels and carton labeling (submitted on August 20, 2025) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information (submitted on January 23, 2025 \\CDSESUB1\EVSPROD\bla761467\0001\m1\us\01-crt-uspi-mk3475a-i-original.docx)

Medication Guide (submitted on January 23, 2025 \\CDSESUB1\EVSPROD\bla761467\0001\m1\us\01-crt-usmg-mk3475a-i-original.docx)

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

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

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(i), 21 CFR 600.3(k)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

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

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

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

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Strength presentation meets recommended labeling practice

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

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

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

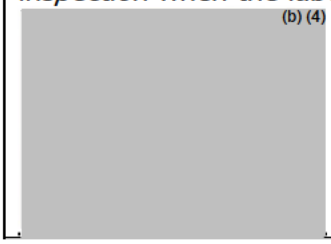
No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *The Sponsor confirms that there is no text on the ferrule and cap overseal of the vials.*

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

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



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

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

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	☐ Yes ☐ No ☒ N/A

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

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

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

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

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

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size Eun in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

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

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

Package[6] Labeling Evaluation

Proper name (package labeling)	Acceptable
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2), 21 CFR 600.3(k)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: On the side panel, revise to read as follows: "Each single-dose vial contains 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa per 2.4 mL". *The Applicant revised as requested.*

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No

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

	☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

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

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

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

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

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

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

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

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

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

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

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: FDA approved labeling is required to use the established names for drugs (i.e., drug products and ingredients) per 21 CFR 299.4. Ensure that the established names for inactive ingredients in your product are the USP/NF monographs titles: histidine, methionine, polysorbate 80, and sucrose. The common name for (b)(4) histidine hydrochloride monohydrate is sufficient.

Revise the ingredient information as follows:
Inactive ingredients: Each 2.4 mL single-dose vial contains histidine (0.7 mg), (b)(4) histidine hydrochloride monohydrate (4.1 mg), methionine (3.6 mg), polysorbate 80 (0.5 mg), sucrose (168 mg), and Water for Injection, USP. *The Applicant revised as requested.*

Inactive ingredients: Each 4.8 mL single-dose vial contains histidine (1.4 mg), (b)(4) histidine hydrochloride monohydrate (8.2 mg), methionine (7.2 mg), polysorbate 80 (1 mg), sucrose (336 mg), and Water for Injection, USP. *The Applicant revised as requested.*

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

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

Comment/Recommendation: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for pembrolizumab and berahyaluronidase alfa products (i.e., there is no specific test method described in regulation for pembrolizumab and berahyaluronidase alfa products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Keytruda Qlex because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable. *Applicant's response: The Sponsor proposes to maintain the statement "No U.S. standard of potency" on the carton. Pembrolizumab is an active ingredient in both Keytruda and MK-3475A. Since this statement is currently on the Keytruda IV carton, the Sponsor proposes to also include it on the carton for MK-3475A.*

Although this statement, "No U.S. standard of potency", currently appears on the carton labeling of the reference product, Keytruda, this inclusion predated the Agency's renewed attention to the labeling requirement in § 610.61(r) as part of FDA's implementation of section 7002(e)(4) of the Biologics Price Competition and Innovation Act of 2009. The absence of the statement for Keytruda Qlex should not be interpreted to mean that the Agency reached different conclusions about whether potency is a factor (within the meaning of § 610.61(r)) for Keytruda Qlex and its reference product. Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable. *The Applicant revised as requested.*

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation: Facility is provided using appropriate qualifying phrase "At:" Revise from "Made in Italy" to "Product of Italy" *The Applicant revised as requested.*

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ Yes ☐ No ☐ N/A

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

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

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Ensure that the package type term "Single-dose vial" is accompanied by and in close proximity to "Discard unused portion" *The Applicant revised as requested.*

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

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

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

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

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

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

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

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

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

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

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

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

Comment/Recommendation: Revised for readability and consistency with other multiple active ingredient biologics. *The Applicant revised as requested.*

---------- DOSAGE FORMS AND STRENGTHS----------

Injection: (3)

- 395 mg pembrolizumab and 4,800 units berahyaluronidase alfa per 2.4 mL (165 mg (b) (4) 2,000 units per mL) (b) (4) in a single-dose vial
- 790 mg pembrolizumab and 9,600 units berahyaluronidase alfa per 4.8 mL (165 mg (b) (4) 2,000 units per mL) in a single-dose vial

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv) *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised the storage instructions for prior to preparation of syringe for administration. *The Applicant revised as requested.*

Revised for readability and relocated the description of the materials of construction to appear with the relevant component. *The Applicant revised as requested.*

Describe the room temperature storage temperature range and confirm if prepared syringe needs to be protected from light. *The Applicant revised as requested. Merck confirms that the prepared syringes do not need to be protected from ambient light.*

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling*	✓ Yes ☐ No

Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	☐ N/A

Comment/Recommendation: Revised for readability and consistency with labeling of other multiple active ingredient biologics in section 3 of PI. *The Applicant revised as requested.*

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revised to "fixed-combination drug product" since this language aligns with terminology in various CDER Guidance documents related to nomenclature and labeling of drug products with two or more drug substances within one dosage form. *The Applicant revised as requested.*

We deleted duplicative information (b) (4) (b) (4) (b) (4) it is not necessary to duplicate (b) (4) in this manner. *The Applicant revised as requested.*

Revised for consistency with other fixed combination drug products containing hyaluronidase for this purpose. *Applicant's response: Merck proposes to retain the statement as originally proposed based on nonclinical study report PD002MK5180 (MK-5180: Analysis of ALT-B4 efficacy using dermal barrier reconstitution assay and trypan blue dispersion assay in BALB/c-Nude mice); please refer to Module 2.2.2.1. The study analyzes the diffusion activity of MK-5180 following intradermal injection by measuring diffusion area on photographed pictures of treated animals. In addition, Merck proposes to clarify that the drug co-administered subcutaneously with berahyaluronidase alfa in this product is pembrolizumab.*
After consultation with Clinical Pharmacology colleagues, the Applicant's proposal was determined to be acceptable.

FDA approved labeling is required to use the established names for drugs (i.e., drug products and ingredients) per 21 CFR 299.4. Ensure that the established names for inactive ingredients in your product are the USP/NF monographs titles: histidine, methionine, polysorbate 80, and

sucrose. The common name for (b) (4) histidine hydrochloride monohydrate is sufficient. *Applicant's response: Merck accepts with revisions to remove the* (b) (4) *histidine hydrochloride monohydrate' for consistency within the revised Keytruda Qlex inactive ingredient list.* Add the pH. *The Applicant added the pH*

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

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

Comment/Recommendation: Revised for readability and consistency with labeling of other multiple active ingredient biologics in section 16 of PI. *The Applicant revised as requested.*

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

Comment/Recommendation: Added your US license #. *The Applicant revised as requested.*

Medication Guide Evaluation

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

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

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

Comment/Recommendation: revised inactive ingredient names to match your prescribing information

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

Comment/Recommendation: relocated your US license number to appear with the manufacturer's statement

Manufactured by: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA
U.S. License No. 0002

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

Prescribing Information (submitted on August 25, 2025
\\CDSESUB1\EVSPROD\bla761467\0037\m1\us\04-crt-uspi-mk3475a-i-original.docx)

Medication Guide (submitted on August 25, 2025
\\CDSESUB1\EVSPROD\bla761467\0037\m1\us\04-crt-usmg-mk3475a-i-original.docx)

Container Labels (submitted on August 20, 2025)

(b) (4)

Carton Labeling (submitted on August 20, 2025)

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

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 8/27/2025 11:37:07AM
GUID: 50814c7000007a3d59329f660d8ddf02

Kun Dong

Digitally signed by Kun Dong
Date: 8/27/2025 12:38:57PM
GUID: 61f1726d00b57ddc42c79e7c5a954539