# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761381Orig1s000
# 761429Orig1s000

# PRODUCT QUALITY REVIEW(S)

# LABELS AND LABELING ASSESSMENT

| | |
|---|---|
| Date of Assessment: | December 23, 2024 |
| Assessor: | Vicky Borders-Hemphill, PharmD<br>Labeling Assessor<br>Office of Product Quality Assessment III (OPQA III) |
| Through: | Faruk Sheikh, PhD<br>Product Quality Assessor<br>OPQA III/Division of Product Quality Assessment XIV |
| Application: | BLA 761381 and BLA 761429 |
| Applicant: | Bristol-Myers Squibb Company<br>Shared Manufacturing Arrangement between Bristol Myers Squibb Company and Halozyme |
| Submission Date: | February 29, 2024 |
| Product: | Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) |
| Dosage form(s): | injection |
| Strength and Container-Closure: | 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) solution 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 December 20, 2024) and container labels and carton labeling (submitted on December 17, 2024) 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 December 20, 2024) and container labels and carton labeling (submitted on December 17, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

## APPENDICES

**Appendix A**: Proposed Labeling

Prescribing Information and Medication Guide (submitted on February 29, 2024 \\CDSESUB1\EVSPROD\bla761381\0001\m1\us\initial-bla-nivo-hyal-markup.pdf)

Container Labels (submitted on February 29, 2024)

(b) (4)



2 Page(s) 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)(1), 21 CFR 600.3(k) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Revise the dosage form from (b) (4) to "Injection". *The Applicant revised as requested.*

| 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)(1), 21 CFR 201.100(e) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (using the qualifying phrase "Manufactured by:")* | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (U.S license number for container bearing a partial label[5])* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** *Under the SMA, Halozyme is responsible for the manufacture of recombinant human hyaluronidase PH20 (rHuPH20) as an intermediate product for further manufacture and Bristol Myers Squibb Company is responsible for the*

[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."

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| *manufacture of efgartigimod drug product co-formulated with rHuPH20 (efgartigimod PH20 SC). The label is small and could be considered a partial label with lack of space to include both manufacturers participating in the SMA.* |

| **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)(1) | ✓ Yes<br>☐ No<br>☐ N/A |

| **Expiration date (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17 | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ 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<br>☐ No<br>☒ N/A |

| **Product Strength (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4) | ✓ Yes<br>☐ No<br>☐ 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)<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

| |
|---|
| **Comment/Recommendation:** Revise the strength presentation as follows: "600 mg and 10,000 units/5 mL (120 mg and 2,000 units/mL)". *The Applicant revised as requested.* |

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

| **Statement: "Rx only" (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |

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

**Comment/Recommendation:** The label is small and would be considered a partial label. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7).

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

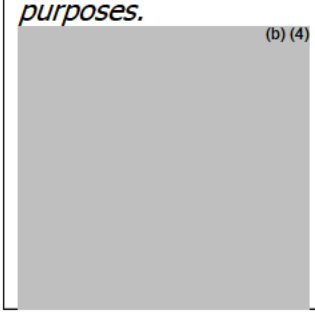
| **No container label (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.60(d) | ☐ Yes<br>☐ No<br>☒ N/A |

| **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<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Confirm there is no text on the ferrule and cap overseal of the vials. *Applicant's response: BMS confirms that there is no text on the ferrule and cap overseal of the nivolumab subcutaneous (SC) injection* (b) (4) *vials.*

| **Visual inspection** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.60(e) | ✓ Yes<br>☐ No<br>☐ 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. *Applicant's response: BMS confirms that there is sufficient area of the vial that remains uncovered by the label to allow for visual inspection when the label is affixed to the vial. There is 5 mm of clear space along the circumference of the vial, throughout the height (full length) of the vial. The photograph illustrates the clear space available for visual inspection for illustration purposes.*




| **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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)* | ✓ Yes<br>☐ No<br>☐ N/A |

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

| **Preparation instructions (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.5(g) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) | ☐ Yes<br>☐ No<br>☒ 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)<br>*USP chapter <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |

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

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

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

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

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

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

**Comment/Recommendation:** Revise from (b) (4) to read as follows: "Dosage: See Prescribing Information". *The Applicant revised similarly as requested.*

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

**Comment/Recommendation:** Consider revising from [redacted] (b) (4) to read as follows: "Refrigerate at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake." to match your prescribing information. *The Applicant revised as requested.*

| **Dispensing container (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.100(b)(7) | ☐ Yes<br>☐ No<br>☒ 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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Revise the dosage form from [redacted] (b) (4) to "Injection". *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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (using the qualifying phrase "Manufactured by:")* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** *Under the SMA, Halozyme is responsible for the manufacture of recombinant human hyaluronidase PH20 (rHuPH20) as an intermediate product for further manufacture and Bristol Myers Squibb Company is responsible for the*

[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.

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| *manufacture of efgartigimod drug product co-formulated with rHuPH20 (efgartigimod PH20 SC). The package label provisions may be met by placing the name, address, and license number of the final product manufacturer and the manufacturer responsible for reporting adverse events on the outer label affixed to the package, and by placing the names, addresses, and license numbers of manufacturers participating in the shared manufacturing arrangement in the product package insert. See Prescribing Information.* |

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

| **Expiration date (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(d), 21 CFR 201.17 | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☒ N/A |

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

| **Number of containers (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(f) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

| |
|---|
| **Comment/Recommendation:** Revise the strength presentation as follows: "600 mg and 10,000 units/5 mL (120 mg and 2,000 units/mL)". *The Applicant revised as requested.* |

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

**Comment/Recommendation:** Consider revising from [redacted] (b) (4) to read as follows: "Refrigerate at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake." to match your prescribing information. *The Applicant revised as requested.*

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

| **Multiple dose containers (recommended individual dose) (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(j) | ☐ Yes<br>☐ No<br>☒ 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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)* | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☒ N/A |

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

**Comment/Recommendation:** Revise only the ingredient list to include the USAN of the drug substance as follows: "Each single dose vial contains 600 mg nivolumab and 10,000 units hyaluronidase (human recombinant) per 5 mL solution". *The Applicant revised as requested.*

We note that the amount of pentetic acid is provided as 0.0985 mg in the 3.2.P.1 submission. OPQ does not currently have (b) (4) rules or policy but refer to (b) (4) in the ORA Lab Manual. (b) (4) (b) (4) (b) (4). Revise the amount of pentetic acid to 0.0985 mg as this aligns with your prescribing information and 3.2.P.1 submission. *The Applicant revised as requested.*

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

| **Minimum potency of product (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.61(r) | ✓ Yes<br>☐ No<br>☐ 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 nivolumab

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| and hyaluronidase products (i.e., there is no specific test method described in regulation for nivolumab and hyaluronidase 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 **Opdivo Qvantig** 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. |

| **Rx only (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |

| |
|---|
| **Comment/Recommendation:** The name, address, and license number of each manufacturer appears in the prescribing information. |

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

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

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

| **Preparation instructions (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references:* Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)<br>*USP General Chapters <7> Labeling* | ☐ Yes<br>☐ No<br>☒ 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)<br>*USP chapter <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |

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

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

| **Spanish-language (Drugs) (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.16 | ☐ Yes<br>☐ No |

| | |
|---|---|
| | ☒ N/A |

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

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

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

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

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

**Comment/Recommendation:** Revise from (b) (4) to read as follows: "Dosage: See Prescribing Information". *The Applicant revised similarly as requested.*

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

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

**Comment/Recommendation:** Revise the medication Guide statement to read: "ATTENTION: Dispense the enclosed Medication Guide to each patient". *The Applicant revised as requested.*

## Prescribing Information Evaluation

**PRESCRIBING INFORMATION**

| **Highlights of Prescribing Information** | |
|---|---|
| **PRODUCT TITLE** | **Acceptable** |
| Regulation: 21 CFR 201.57(a)(2) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Remove the brackets surrounding the four-letter suffix. *The Applicant revised as requested.*

| **Highlights of Prescribing Information** | |
|---|---|
| **DOSAGE AND ADMINISTRATION** | **Acceptable** |
| *Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions* | ☐ Yes<br>☐ No<br>☒ 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<br>☐ No<br>☐ 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)<br>*USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Revise strength presentation as follows: Injection: 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL) in a single-dose vial. *The Applicant revised as requested.*

| Full Prescribing Information | |
|---|---|
| **2 DOSAGE AND ADMINISTRATION** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(3)(iv)<br>*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<br>☐ No<br>☐ 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*<br>Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023) | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Revised from (b) (4) to "for one-time use only" for readability. *The Applicant revised as requested.*
*The Applicant revised the verbatim visually inspection statement and noted that "We acknowledge the request for the verbatim statement from the CFR. BMS would, however, like to retain the more concise statement, which conveys the same requested actions of the healthcare professional. We note that FDA applies some flexibility with CFR language; the Tecentriq Hybreza USPI (approved in Sep 2024) does not contain such text.". OPQA III Labeling does not object.*

OPQA III revised to provide the name of the administration device with corresponding materials of construction (e.g., polypropylene and polycarbonate syringes). OND removed the other proposed materials of construction and provided comment to applicant "As no administration instructions are provided in the USPI for subcutaneous infusion sets, we have deleted the compatibility information for these materials.". *Applicant's response: From BMS: Subcutaneous infusion sets were used during the CA20967T study and the list of compatible materials for these sets were described in module 3.2.P.2.6. BMS proposes to maintain this list of compatible materials and further proposes to include subcutaneous infusion sets as an administration option. Language has been added to support the use of the winged/butterfly set. As mentioned in an earlier comment, this set was used Checkmate -67T. The set reduced nurse strain/fatigue and increases patient comfort, relative to standard needle.". OPQA III Labeling does not object and defers to OND clinical for the inclusion of "or subcutaneous administration set (e.g., winged/butterfly)".*

Revise to include the name of the administration device with corresponding materials of construction. *The Applicant revised as requested.*

Preparation

No incompatibilities were observed between OPDIVO QVANTIG and polypropylene and polycarbonate syringes, or between OPDIVO QVANTIG and polyethylene, polyurethane, polyvinyl chloride, and fluorinated ethylene propylene subcutaneous administration sets.

Provide the time that it takes to reach room temperature. *Applicant's response: From BMS: As settings for preparing OPDIVO QVANTIG may vary from site to site, providing a time to reach room temperature may not be appropriate for each site. Thus, consistent with the recently approved Tecentriq Hybreza USPI, we propose to keep the recommendation as proposed. Furthermore, as OPDIVO QVANTIG is intended for HCP administration by trained professionals who routinely administer such products and is not intended for self-administration by a patient, we believe this additional information is not needed. OPQA III Labeling does not object.*

Revised the hold time limit for syringe storage from (b) (4) to 48 hours. *Applicant's response: As provided in our response to the FDA IR dated July 29, 2024 (Q1), BMS considers the submitted microbiological stability data sufficient to support the storage of the prepared syringe for up to (b) (4) at 2-8°C, as initially proposed in the BLA. At the time, BMS proposed a 48-hour storage period in response to the follow-up FDA IR dated August 28, 2024 (Q1)* (b) (4) (b) (4) (b) (4) *BMS respectfully requests that the FDA consider* (b) (4) *our proposal to revise the storage duration of the prepared syringe to* (b) (4) *at 2-8°C. OPMA response: Data to support extension of storage time should be submitted in a future supplement.*

| Full Prescribing Information | |
|---|---|
| **3 DOSAGE FORMS AND STRENGTHS** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(4) | ✓ Yes<br>☐ No<br>☐ 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)<br>*USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Revise strength presentation as follows: 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL (120 mg/2,000 units per mL), as a clear to opalescent, colorless to yellow solution in a single-dose vial. *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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Revise to include the USAN of the drug substance "hyaluronidase (human recombinant) in the drug substance paragraph and the drug product ingredient list. *The Applicant revised as requested.*
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.*
Added the dosage form. *The Applicant revised as requested.*
(b) (4) is an outdated package type term. This has been revised to "single-dose vial". *The Applicant revised as requested.*
Added the route of administration "for subcutaneous use". *The Applicant revised as requested.*
Revised the appearance of the solution to align with section 2.4. *The Applicant revised as requested.*

| |
|---|
| Revise the amount of pentetic acid from (b) (4) to "0.0985 mg" as this aligns with your 3.2.P.1 submission. *The Applicant revised as requested.*<br>Add the pH of the solution. *The Applicant added "5.5 to 6.5".* |

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

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

| |
|---|
| **Comment/Recommendation:** Revised for readability and for consistent presentation of strength. *The Applicant revised as requested.* |

| **Full Prescribing Information** | |
|---|---|
| **MANUFACTURER INFORMATION** | **Acceptable** |
| Regulations: 21 CFR 201.100(e), 21 CFR 201.1 | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☒ N/A |

| |
|---|
| **Comment/Recommendation:** Per the Shared manufacturing arrangement, add Halozyme Therapeutics, Inc's name address and US license number to the manufacturer's information section. *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<br>☐ No<br>☐ N/A |

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

| MEDICATION GUIDE | |
|---|---|
| **MANUFACTURER INFORMATION** | **Acceptable** |
| 21 CFR 208.20(b)(8)(iii) | ✓ Yes<br>☐ No<br>☐ 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<br>☐ No<br>☒ N/A |

**Comment/Recommendation:** Per the Shared manufacturing arrangement, add Halozyme Therapeutics, Inc's name address and US license number to the manufacturer's information section. *The Applicant revised as requested.*



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

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 12/23/2024 08:08:54AM
GUID: 50814c7000007a3d59329f660d8ddf02

Faruk Sheikh

Digitally signed by Faruk Sheikh
Date: 12/23/2024 08:30:07AM
GUID: 508da6da00026541bce7d8a146aa4138

# BLA Executive Summary Addendum
# Assessment Date: November 15, 2024
# Addendum Date: December 16, 2024

This addendum corrects the "Stability Option" listed on Page 4 of the Office of Pharmaceutical Quality (OPQ) BLA Executive Summary. The "Stability Option" should include a protocol for extension of expiration dating of nivolumab drug substance but was inadvertently listed as "N/A" in the OPQ BLA Executive Summary dated November 15, 2024. This correction does not change the overall recommendations or conclusions of the OPQ BLA Executive Summary dated November 15, 2024.

## 1. Application/Product Information

| | |
|---|---|
| **BLA number** | 761381/761429 |
| **Submission Type** | Original Submission<br><br>BLA 761381/761429 is a final product Biologics License Application in a shared manufacturing arrangement with BLA 761313 for hyaluronidase "for further manufacturing". |
| **Regulatory Pathway** | 351 (a) |
| **Associated IND/BLA** | • IND 138302<br>• IND 150904<br>• BLA 761313 for hyaluronidase (human Recombinant) for further manufacturing use<br>• BLA 761234 for Opdualag (nivolumab and relatlimab-rmbw), includes supportive Chemistry, Manufacturing, and Controls information related to the nivolumab drug substance process |
| **Review Designation** | Standard Review |
| **Applicant** | Bristol Myers Squibb (BMS) |
| **Indication** | • Advanced Renal Cell Carcinoma<br>• Adjuvant Treatment of Melanoma<br>• Unresectable or Metastatic Melanoma<br>• Neoadjuvant Treatment of Resectable NSCLC<br>• Metastatic Non-Small Cell Lung Cancer<br>• Squamous Cell Carcinoma of the Head and Neck |

| | |
|---|---|
| | • Urothelial Carcinoma<br>• Microsatellite Instability-High or Mismatch Repair Deficient Metastatic Colorectal Cancer<br>• Hepatocellular Carcinoma<br>• Esophageal Cancer<br>• Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma<br>**Indications to be included is pending OND review.* |
| **Rx/OTC dispensed** | Rx |
| **Drug Product Name** | **Proprietary Name**<br><br>Opdivo Qvantig |
| | **Non-proprietary Name/Code Name**<br><br>Nivolumab and hyaluronidase-nvhy/BMS-986298 and rHuPH20 |
| | **OBP Naming**<br><br>COMBINATION: MAB HUMAN (IGG4) ANTI Q15116 (PDCD1_HUMAN) [BMS986298]; RPROTFRAG P38567 (HYALP_HUMAN) HYALURONIDASE PH-20 [RHUPH20] |
| **Drug Product Description** | Nivolumab subcutaneous (SC) is fixed combination drug product (DP) provided as a sterile, preservative-free, clear to opalescent, colorless to yellow solution, that may contain a few translucent-to-white particles. Each single-dose vial contains 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL. Nivolumab SC DP is formulated with 7.75 mg histidine, 10.5 mg histidine hydrochloride monohydrate, 3.73 mg methionine, 0.0985 mg pentetic acid, 2.50 mg polysorbate 80, and 428 mg sucrose per 5 mL, to a target pH of (b) (4).<br><br>Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed cell death-1 (PD-1) receptor, blocks interaction with its ligands PD-L1 and PD-L2, and reduces PD-1 pathway-mediated inhibition of the immune response including |

| | | | |
|---|---|---|---|
| | the anti-tumor immune response. The IgG4 heavy chain includes a S221P mutation to increase IgG4 stability.<br><br>Hyaluronidase (recombinant human) is a glycosylated single-chain protein that depolymerizes the gel-like hyaluronan (hyaluronic acid) at the site of injection resulting in a decreased resistance to fluid flow and a transient increase in permeability of the local subcutaneous tissue to support the new route of administration. | | |
| **Dosage Form** | Liquid | | |
| **Strength** | 600 mg nivolumab and 10000 Units hyaluronidase / 5 mL | | |
| **Route of Administration** | Subcutaneous (SC) injection | | |
| **Primary Container Closure System** | Vial | | |
| **Device Information** | None | | |
| **Co-packaged Product Information** | None | | |
| **OPQ Review Team** | **Discipline** | **Primary** | **Secondary** |
| | Drug substance | Faruk Sheikh | Phillip Angart |
| | Drug product | | |
| | Immunogenicity Assay | | |
| | Facility | DS: Richard Ledwidge<br><br>DP: Abigail Marella | Madushini Dharmasena |
| | Microbiology | | |

| | | |
|---|---|---|
| | RBPM | Kelly Ballard |
| | ATL | Phillip Angart |
| **OPQ Issued Consults** | None | |

## 2. Recommendation and Conclusion on Approvability
## Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLAs 761381 and 761429 for Opdivo Qvantig manufactured by Bristol Myers Squibb. The data submitted in this application are adequate to support the conclusion that the manufacture of Opdivo Qvantig 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 [nivolumab]:** Bristol-Myers Squibb Company, 38 Jackson Road, Devens, MA 01434, USA; FEI: 3008455069
- **Drug Product:** (b) (4)

**b. Fill size and dosage form:** Opdivo Qvantig is supplied as a single-dose vial of 600 mg nivolumab and 10,000 units hyaluronidase per 5 mL (120 mg and 2,000 units per mL) as a sterile liquid for subcutaneous injection.

**c. Dating Period:**

- **Drug Product:** 36 months at 2 °C to 8 °C, protected from light
- **Drug Substance [nivolumab]:** (b) (4)
- **For packaged products:** Not packaged
- **Stability Option:** We have approved the stability protocol in your license application for the purpose of extending the expiration dating of your nivolumab drug substance under 21 CFR 601.12.

**d. Exempt from lot release:**

- Yes
- Rationale, if exempted: specified product
  Opdivo Qvantig is exempted from lot release per FR 95-29960.

**e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable**

*The following post-marketing commitment (PMC) was discussed and agreed to by the Applicant during the BLA review.*

1. Establish and validate/qualify an appropriate method (existing or new), for determining the number and size of product-related visible particles in nivolumab subcutaneous injection drug product and implement the method for evaluation of visible particles in nivolumab subcutaneous injection drug product stability testing.

   Final Report Submission: December 19, 2025

## 4. Basis for Recommendation

### a. Summary:

Opdivo Qvantig (nivolumab and hyaluronidase-nvhy) is a fixed-combination of nivolumab and hyaluronidase (human recombinant) provided as a single-use vial of 600 mg nivolumab and 10,000 units hyaluronidase in 5 mL as a sterile liquid for subcutaneous injection. Nivolumab and hyaluronidase-nvhy is being approved as a Biologics License Application for final product (BLA-FP) in a shared manufacturing arrangement with BLA 761313, a Biologics License Application for further manufacture (BLA-FFM), for Hyaluronidase (human recombinant) for further manufacturing use in accordance with the FDA guidance for industry *Cooperative Manufacturing Arrangements for Licensed Biologics* (November 2008). A letter of authorization permitting cross-reference to BLA 761313 was included in the BLA-FP submission along with a shared manufacturing arrangement outlining responsibilities between Halozyme and BMS for hyaluronidase (human recombinant).

Opdivo Qvantig leverages indications from the intravenous formulation of nivolumab under BLA 125554 based on the clinical bridge established between the intravenous and subcutaneous formulations. BLA 761429 is a Type 9 submission intended to add two indications (neoadjuvant and adjuvant treatment of resectable non-small cell lung cancer and urothelial carcinoma) to the Opdivo Qvantig label based on the clinical bridge between the intravenous and subcutaneous formulations of nivolumab. Both indications were added to the intravenous formulation of nivolumab under BLA 125554 during the review cycle for BLA 761381. All CMC information to support BLA 761429 was cross-referenced to BLA 761381. Both BLA 761381 and BLA 761429 were reviewed simultaneously. Therefore, the review of BLA

761381 is applicable to BLA 761429 and the same review applies to both BLAs from product quality perspective.

Nivolumab is a human monoclonal IgG4 antibody consisting of four polypeptide chains; two identical heavy chains and two identical kappa light chains linked through inter-chain disulfide bonds. The heavy chain includes S221P mutation which is known to impart increased stability. Nivolumab is a programmed cell death protein 1 (PD-1) antagonist. Engagement of the PD-1 receptor by its ligands PD-L1 and PD-L2 allows tumors to evade immune mediated destruction by inhibition of T-cell proliferation, survival and cytokine secretion. Nivolumab blocks the interaction of the PD-1 receptor inhibiting multiple PD-1 ligand interactions and restores T-cell responsiveness and the ability to mount a direct T-cell immune attack against tumor cells. The potency of nivolumab is controlled with a binding ELISA assay that measures binding to the PD-1 receptor and a cell-based potency assay with Jurkat E6.1 T-cells expressing the human PD-1 receptor and Raji B-cells expressing human PD-L1 that measures interleukin 2 secretion upon disruption of PD-1/PD-L1 and Jurkat E6.1 T-cell activation. Potency in both assays is measured relative to a reference standard.

Hyaluronidase (human recombinant) is a glycosylated soluble fragment of human hyaluronidase (PH20) that increases permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan allowing for larger subcutaneous injection volumes. Hyaluronidase potency is controlled with an enzymatic activity assay that measures the hyaluronic acid cleavage. Potency is measured relative to a standard curve of the assay reference standard and reported in units of activity per mL of drug product.

The nivolumab drug substance (DS) manufacturing process consists of

The nivolumab and hyaluronidase-nvhy DP manufacturing process includes (b) (4)

Nivolumab and hyaluronidase-nvhy DP is a is fixed combination DP provided as a sterile, preservative-free, clear to opalescent, colorless to yellow solution, that may contain a few translucent-to-white particles. Each 5 mL single-dose vial contains 600 mg nivolumab, 10,000 units hyaluronidase (human recombinant), 7.75 mg histidine, 10.5 mg histidine hydrochloride monohydrate, 3.73 mg methionine, 0.0985 mg pentetic acid, 2.5 mg polysorbate 80, and 428 mg sucrose to a target pH of (b) (4) Nivolumab and hyaluronidase-nvhy DP is provided in a (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum cap and stored at the long-term storage condition of 2 °C to 8 °C, protected from light.

The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for the DS and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. One post-marketing commitment (PMC) is recommended for inclusion in the approval letter to validate/qualify a method for the determination and size and number of proteinaceous visible particles in nivolumab and hyaluronidase-nvhy DP stability samples to ensure that observed particles remain within the clinical experience. The current method for visual inspection is semi-quantitative and capable of determining product characteristics but not particle sizes. This method is suitable for the control of visible particles until additional qualification work of the current method is performed or a new method is developed.

The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The DP sterilized using a validated filtration process (b) (4)

(b) (4)

The pre-license inspection (PLI) of Bristol-Myers Squibb Company in Devens, MA (FEI: 3008455069), responsible for manufacturing and testing of nivolumab DS, was waived based on satisfactory inspection history. A Remote Regulatory Inspection (RRA) was conducted for (b) (4) responsible for manufacturing and testing of nivolumab and hyaluronidase-nvhy DP. No observations were noted at the completion of the assessment.

The overall nivolumab and hyaluronidase-nvhy control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The manufacturing processes and overall control strategies for nivolumab and hyaluronidase-nvhy are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The BLA is recommended for approval from a product quality, facility, microbiology, and sterility assurance perspectives.

Individual assessments for each OPQ subdiscipline are located in separate documents in Panorama.

**b. Subdiscipline Recommendation:**

| | | |
|---|---|---|
| **Drug Substance** | **-** | **Adequate** |
| **Drug Product** | **-** | **Adequate with PMCs/PMRs** |
| **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 nivolumab and hyaluronidase (i.e., there is no specific test method described in regulation for nivolumab and hyaluronidase that establishes an official standard of potency). We next considered whether potency is a factor for nivolumab and hyaluronidase 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 Opdivo Qvantig for purposes of § 610.61(r) because lot variability is not a concern for Opdivo Qvantig as Opdivo Qvantig'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:**

i. Protocols approved:

1. (b) (4)
2.
3.
4.
5.
6.
7.

ii. Residu

iii. Future inspection points to consider: None

**c. Drug Product:**

i. Protocols approved:
   1. Stability protocol for drug product PPQ batches
   2. Real time leachables study
   3. Annual post approval stability protocol for nivolumab SC injection

ii. Residual risk: Refer to Sections 3.e and 4.a

iii. Future inspection points to consider: None

**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.

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

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/s/

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PHILLIP A ANGART
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