CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761234Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	March 17, 2022
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Phillip Angart, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 2
Application:	BLA 761234
Applicant:	Bristol-Myers Squibb Company
Submission Date:	May 4, 2021
Product:	Opdualag (nivolumab and relatlimab-rmbw)
Dosage form(s):	Injection
Strength and Container-Closure:	240 mg nivolumab and 80 mg relatlimab per 20 mL (12 mg and 4 mg per mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information/medication guide, container labels, and carton labeling submitted on March 17, 2022 were assessed and found to be acceptable (see Appendix C) from an OBP 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/medication guide, container labels, and carton labeling submitted on March 17, 2022 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide (submitted on October 5, 2021 \\CDSESUB1\evsprod\bla761234\0024\m1\us\04oct2021-advanced-melanoma-relat-nivol-rmbw-pro.pdf)

Container Labels (submitted on October 5, 2021)

Carton Labeling (submitted on October 5, 2021)

(b) (4)

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(h)(2)(i)(1)(i)	✓ 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: Revise so that the active ingredients appear in alphabetical order "(nivolumab and relatlimab-rmbw)" *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(h)(2)(i)(1)(iv), 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(h)(2)(i)(1)(iii)	✓ Yes ☐ No

[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."

	☐ N/A

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, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ 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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise strength presentation to "240 mg and 80 mg/20 mL (12 mg and 4 mg/mL)" so that it coincides with the active ingredient names appearing in alphabetical order *The Applicant revised as requested*

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ 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

Comment/Recommendation: Add the required Medication Guide statement to the principal display panel of the vial label
Applicant's response: The required Medication Guide statement is intentionally placed on the package label because the container label is too small to include it [per 21 CFR 610.60(a)(7) …except where the container label is too small, the required statement may be placed on the package label]

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. *Applicant's response: BMS confirms that there is no text on the seal (cap or ferrule) 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
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 10 mm of clear space along the circumference of the vial, throughout the height of the vial.

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ 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

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 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-*	✓ Yes ☐ No ☐ N/A

512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic	

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: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *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

Comment/Recommendation: Revise Statement of Dosage to read "Dosage: see Prescribing Information." *The Applicant revised as requested*

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ 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

Comment/Recommendation: Revise the storage statement to "The vial must be refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze or shake." *The Applicant revised as requested*

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

Other (package labeling)	**Acceptable**
	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Remove (b) (4) statement
The Applicant revised as requested

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)	✓ 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: Revise so that the active ingredients appear in alphabetical order "(nivolumab and relatlimab-rmbw)" *The Applicant revised as requested*

[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.

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 ☐ 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

Comment/Recommendation: Ensure that the lot number appears on the carton labeling
The Applicant revised as requested

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

Comment/Recommendation: Ensure that the expiration date appears on the carton labeling
The Applicant revised as requested

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise strength presentation to "240 mg and 80 mg/20 mL (12 mg and 4 mg/mL) so that it coincides with the active ingredient names appearing in alphabetical order *The Applicant revised as requested*

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

Comment/Recommendation: Revise the storage statement to "Storage: The vial must be refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze or shake." *The Applicant revised as requested*

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	✓ 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: Revise the contents statement to provide the net quantity, the ingredients to appear in alphabetical order, and to align with the prescribing information as follows: "One 20 mL single-dose vial provides 240 mg of nivolumab and 80 mg of relatlimab. Each mL contains 12 mg of nivolumab, 4 mg of relatlimab, and histidine (1.1 mg), L-histidine hydrochloride monohydrate (2.7 mg), pentetic acid (0.008 mg), polysorbate 80 (0.5 mg), sucrose (85.6 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

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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

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

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* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ 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: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *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

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: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *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

Comment/Recommendation: Revise Statement of Dosage to read "Dosage: See prescribing information." *The Applicant revised as requested*

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

Other (package labeling)	**Acceptable**
	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Remove "Fixed Dose Combination" statement *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 ☐ 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

Comment/Recommendation: Revise so that the active ingredients appear in alphabetical order "(nivolumab and relatlimab-rmbw)" *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 ☐ 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: Revise to "Injection: 240 mg of nivolumab and 80 mg of relatlimab per 20 mL (4 mg and 12 mg 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)] *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	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise so that the active ingredients appear in alphabetical order *The Applicant revised as requested*

The intravenous container materials have been added for clarity "OPDUALAG is compatible with di(2-ethylhexyl)phthalate (DEHP)-plasticized polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), polyolefin (PO), and PVC intravenous bags." *The applicant agrees with FDA regarding including intravenous material type. However, DEHP PVC covers PVC which is included in the list, therefore BMS deleted the second instance of PVC in the list. OBP agreed.*
The filter material types have been added for clarity "low protein binding in-line polyethersulfone (PES), nylon, or polyvinylidene fluoride (PVDF) filter (pore size of 0.2 micrometer to 1.2 micrometer)." *The Applicant revised as requested*

Clarify if the storage timeframe of 24 hours under refrigeration for the prepared intravenous infusion solution includes the time allowed for equilibration of the infusion bag to room temperature prior to infusion. If so, we added to the proposed storage instructions "under refrigeration…for no more than 24 hours from the time of preparation, which includes the time allowed for equilibration of the infusion bag to room temperature and the duration of the infusion. Discard the prepared solution if not used within 24 hours from the time of preparation." *The Applicant revised as requested*

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 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: Revise so that the active ingredients appear in alphabetical order *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)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Deleted (b) (4) since this first paragraph discusses the drug substance *The Applicant revised as requested*
Added the pharmacological classes *The Applicant revised as requested*
Added the dosage form *The Applicant revised as requested*
Added the route of administration *The Applicant revised as requested*

Revise so that the active ingredients appear in alphabetical order *The Applicant revised as requested* Revised inactive ingredients to appear in alphabetical order and revised to "L-histidine hydrochloride monohydrate" *The Applicant revised as requested* Requested the addition of the pH *The Applicant provided as requested* Deleted (b) (4) and retained "few" to describe particles for consistency with section 2 *The Applicant revised as requested*

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: Added the proper name to the first paragraph "(nivolumab and relatlimab-rmbw)" *The Applicant revised as requested* Deleted (b) (4) and (b) (4) *The Applicant revised as requested* Added the route of administration *The Applicant revised as requested* Relocated the strength, package type term, and NDC number (b) (4) to the paragraph above *The Applicant revised as requested* Revise the storage statement to "Store OPDUALAG refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze or shake." *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

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

Comment/Recommendation: Revise so that the active ingredients appear in alphabetical order *The Applicant revised as requested*

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 active and inactive ingredients to appear in alphabetical order *The Applicant revised as requested*

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

Patient Information Labeling Evaluation (N/A)

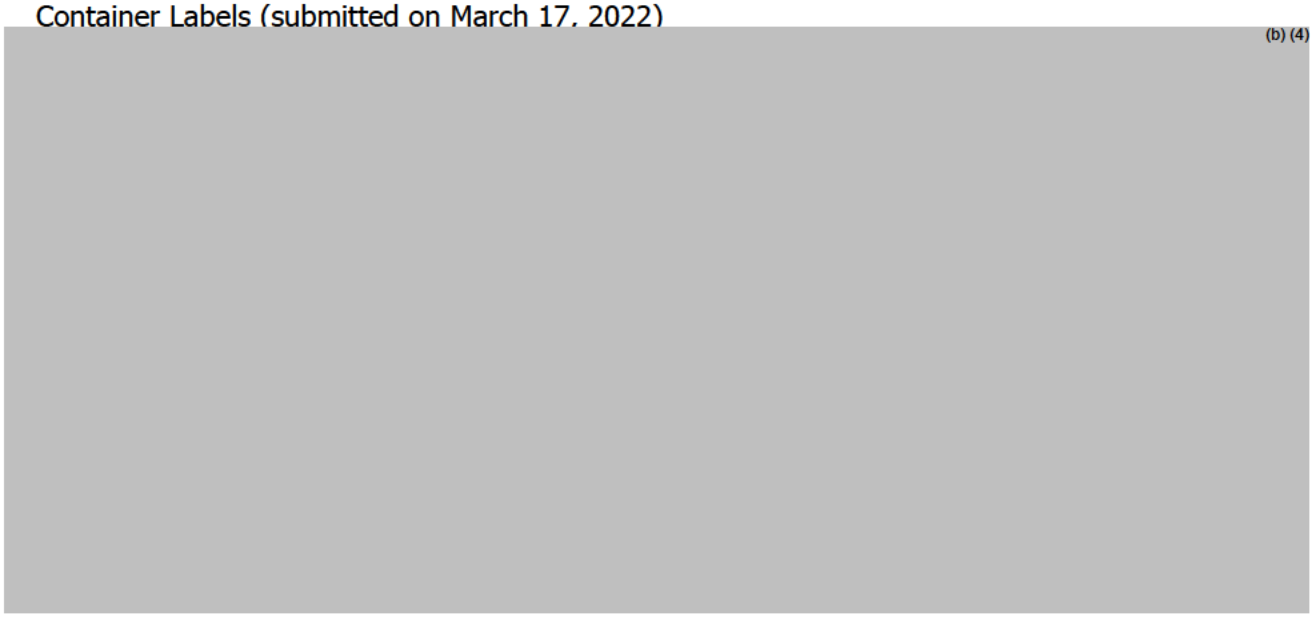
Instructions for Use Evaluation (N/A)

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information/Medication Guide (submitted on March 17, 2022 \\CDSESUB1\evsprod\bla761234\0058\m1\us\16mar2022-advanced-melanoma-nivol-relat-rmbw-pro.pdf)

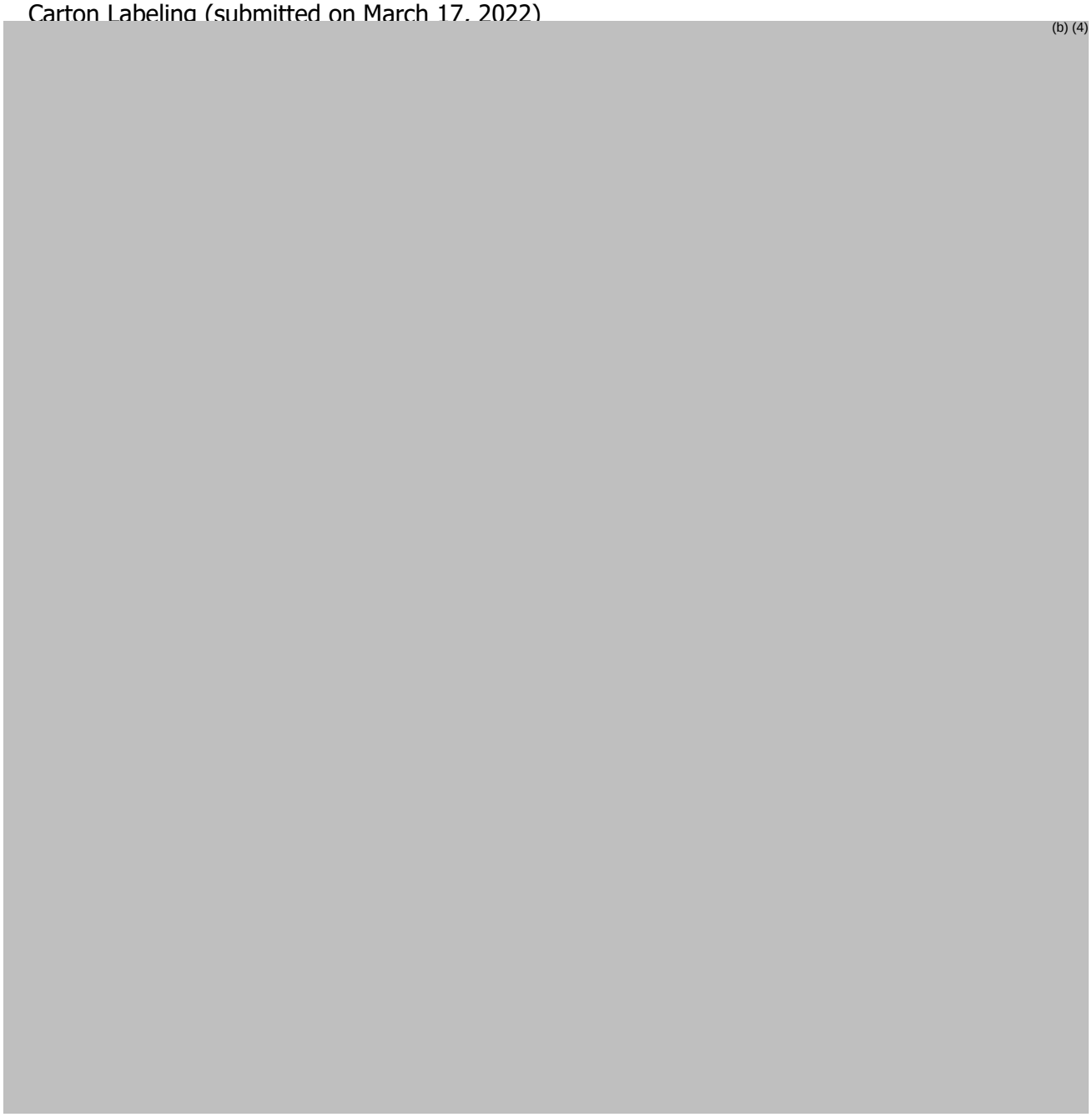
Container Labels (submitted on March 17, 2022)

(b) (4)



Carton Labeling (submitted on March 17, 2022)

(b) (4)



Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 3/17/2022 02:04:43PM
GUID: 50814c7000007a3d59329f660d8ddf02

Phillip Angart

Digitally signed by Phillip Angart
Date: 3/17/2022 02:21:11PM
GUID: 5bae72df003e500e3647d7cc5bd3b42f

Recommendation: Approval

BLA Number: 761234
Application Technical Lead Assessment Number: 1
Assessment Date: January 19, 2022

Drug Name/Dosage Form	Opdualag – nivolumab and relatlimab-rmbw/ injection
Strength/Potency	240 mg nivolumab and 80 mg relatlimab per 20 mL
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indication	Treatment of adults and pediatric patients 12 years or older with unresectable or metastatic melanoma
Applicant/Sponsor	Bristol-Myers Squibb Company
US agent, if applicable	N/A

Product Overview:

Opdualag is a fixed dose combination product of nivolumab and relatlimab at a 3:1 protein-mass ratio. Relatlimab is a human IgG4 monoclonal antibody that binds to the lymphocyte activation gene 3 (LAG-3) receptor, blocks interaction with its ligands, and reduces LAG-3 pathway-mediated inhibition of the immune response. Nivolumab is a human 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. Combined relatlimab (anti-LAG-3) and nivolumab (anti-PD-1) results in increased T-cell activation and anti-tumor response that is greater than the effects of either antibody alone. Both drug substances are produced by recombinant DNA technology in Chinese hamster ovary cells. Opdualag is supplied as 240 mg of nivolumab and 80 mg of relatlimab in a 20 mL single-dose vial for intravenous use.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Phillip Angart	DBRRII/OBP/OPQ
Drug Product		
Immunogenicity		
Labeling	Vicky Borders-Hemphill	DBRRII/OBP/OPQ
Facility	Michael Shanks/Virginia Carroll	DBM/OPMA/OPQ
Microbiology	Reyes Candau-Chacon/Virginia Carroll	DBM/OPMA/OPQ
Regulatory Business Process Manager	Anika Lalmansingh	RBPMB2/DRBPM1/OPRO/OPQ
Application Team Lead	Anjali Shukla	DBRRII/OBP/OPQ

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Christina Leach	OND/ORO/DRO-OOD
Cross-disciplinary Team Lead	Jamie Brewer	OND/OOD/DO3
Medical Officer	Leslie Doros and Leigh Marcus	OND/OOD/DO3
Pharmacology/Toxicology	Elizabeth Sphalski/Matthew Thompson	OND/OOD/DHOT
Clinical Pharmacology	Hongfei Zhang/Hong Zhao	OTS/OCP/DCPII
	Yangbing Li/Jiang Liu	OTS/OCP/DPM
Statistics	Jiaxin Fan/Joyce Cheng	OTS/OB/DBV5

1. Names:

a. Proprietary Name: OPDUALAG
b. Trade Name: OPDUALAG
c. Non-Proprietary Name/USAN: nivolumab and relatlimab-rmbw
d. CAS Name: 946414-94-4 (for nivolumab) and 1673516-98-7 (for relatlimab)
e. Common Name: N/A
f. INN Names: nivolumab, relatlimab
g. Compendial Name: N/A
h. OBP systematic name: COMBINATION: MAB HUMAN (IGG4) ANTI Q15116 (PDCD1_HUMAN) ([BMS936558]; MAB HUMANIZED (IGG4) ANTI P18627 (LAG3_HUMAN) [BMS986016]

Submissions Assessed:

Submission(s) Assessed	Document Date
761234/ SDN 1	May 4, 2021
761234/ SDN 2	May 7, 2021
761234/ SDN 4	May 25, 2021
761234/ SDN 5	June 4, 2021
761234/ SDN 6	June 15, 2021
761234/ SDN 7	July 19, 2021
761234/ SDN 8	July 30, 2021
761234/ SDN 10	August 9, 2021
761234/ SDN 11	August 13, 2021
761234/ SDN 16	September 10, 2021
761234/ SDN 21	September 23, 2021
761234/ SDN 25	October 8, 2021
761234/ SDN 30	October 28, 2021
761234/ SDN 33	November 24, 2021
761234/ SDN 36	December 3, 2021
761234/ SDN 38	December 10, 2021
761234/ SDN 42	December 22, 2021
761234/ SDN 44	January 7, 2022
761234/ SDN 48	January 18, 2022

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

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed	Comments
(b) (4)	V		(b) (4)	3	N/A	N/A	N/A
	III			2,3	Adequate	April 1, 2021	*Information to assess* (b) (4)
	III			3	N/A	N/A	*validation was previously assessed and found adequate. No assessment required at this time for other aspects as the relevant information related to compatibility with the product was in the BLA.*
	V			2,3	Adequate	January 29, 2020	
	V			2,3	Adequate	June 24, 2019	
	II			2	Adequate	August 6, 2021	Adequate

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application; therefore, the DMF did not need to be assessed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
		(b) (4)
IND	136382	IND for fixed dose combination of nivolumab and relatlimab
BLA	125554	BLA for Opdivo (nivolumab)

3. Consults: no consults requested by OPQ

4. Environmental Assessment of Claim of Categorical Exclusion:
Bristol Myers Squibb Company is requesting a categorical exclusion from the preparation of an environmental assessment (EA) for BMS-986213 (fixed dose combination of nivolumab and relatlimab) according to section 505(b) of the Federal Food, Drug, and Cosmetic Act. The subject of the proposed action will not significantly affect the quality of the environment and meets the requirements for a categorical exclusion from submitting an environmental assessment under 21 CFR 25.31(c). The drugs are proteins (monoclonal antibodies) that are expected to rapidly degrade to amino acids and mineralize to carbon dioxide. In addition, to Bristol Myers Squibb Company's knowledge, no extraordinary circumstances exist, as referenced in 21 CFR 25.15(d). It is not derived from any wild-sourced plant and/or animal material 21 CFR 25.21(b).

Assessor comment:
The Applicant's request for categorical exclusion from preparation of an environmental assessment is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Approval

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761234 for Opdualag manufactured by Bristol-Myers Squibb Company. The data submitted in this application are adequate to support the conclusion that the manufacture of Opdualag 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.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance:
    Bristol-Myers Squibb Company
    38 Jackson Road
    Devens, Massachusetts 01434
    USA
    FEI: 3008455069
  - Drug Product:
    (b) (4)
- Fill size and dosage form
  240 mg nivolumab and 80 mg relatlimab per 20 mL (12 mg and 4 mg per mL) in a single-dose vial, injection
- Dating period:
  - Drug Product: 36 months: 2-8°C
  - Drug Substance:
    - Nivolumab (b) (4) (b) (4) months: (b) (4) °C
    - Relatlimab: (b) (4) months : (b) (4) °C
  - For packaged products: Not packaged
  - Stability Option :
    - We have approved the stability protocols in your license application for the purpose of extending the expiration dating of your drug substances under 21 CFR 601.12.

- Exempt from lot release:
    - Yes
    - Rationale, if exempted: specified product
      Note: Opdualag is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations: Opdualag is a combination of nivolumab, a PD-1 receptor blocking antibody, and relatlimab, a LAG-3 blocking antibody. Opdualag is indicated for the treatment of adults and pediatric patients 12 years or older with unresectable or metastatic melanoma. The manufacturing process and overall control strategy for the drug substances and drug product are sufficient to ensure consistent manufacture of product that is pure and potent. The immunogenicity assays are suitable and sensitive to detect anti-drug antibodies to Opdualag. During the review cycle, the Applicant agreed to post-marketing commitments to re-evaluate the acceptance criteria for potency of relatlimab after 30 lots of drug product have been manufactured and to develop an endotoxin release method that is able to reliably detect endotoxin in the drug product (refer to Section I.D below).
The current relatlimab potency acceptance criteria are sufficient to ensure adequate quality and safety of Opdualag for the initial marketed product. However, these acceptance criteria are based on the clinical and limited manufacturing experience provided in the BLA and do not allow for a robust statistical analysis of the data. Re-evaluation after additional manufacturing experience has been gained can facilitate improved specifications.
The current endotoxin detection method is not able to reliably detect endotoxin from the drug product due to low endotoxin recovery. The Applicant will implement the rabbit pyrogen test as an additional interim release test until a reliable endotoxin detection method is available.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

Post-Marketing Commitments:

1. Re-evaluate the lot release and stability acceptance criteria for the potency (cell-based) - relatlimab test for relatlimab drug substance and Opdualag drug product after the manufacture of 30 drug product lots with the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report by January 2027.

2. To develop an endotoxin release method for the drug product which mitigates the low endotoxin recovery (LER) effect and to submit the results of the LER study performed at (b) (4) with 3 lots of drug product, the endotoxin method qualification with 3 lots of drug product and the updated endotoxin method. The updated endotoxin method will replace the rabbit pyrogen testing upon approval of the supplement. Due September 2022.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 below is a summary of critical quality attributes and the associated control strategies for

attributes that are relevant to both drug substance and drug product. For additional information, see the OPQ primary technical memorandums in Panorama.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)	Risk	Origin	Control Strategy	Other
Potency	Efficacy	Manufacturing process, storage	(b) (4)	The Applicant agreed to a PMC to re-evaluate relatlimab potency acceptance criteria for relatlimab DS and Opdualag DP when 30 lots of DP have been manufactured.
Size variants (HMW and LMW species)	Safety and efficacy	Manufacturing process, storage		N/A
Protein concentration	Efficacy	Manufacturing process		N/A

B. Drug Substance Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

Tables 2a and 2b below provide summaries of the identification, risk, and lifecycle management for nivolumab (b) (4) drug substance and relatlimab drug substance CQAs respectively that derive from the drug substance manufacturing processes and general drug substance attributes. For additional information, see the OPQ primary technical memorandums in Panorama.

i. Nivolumab (b) (4) drug substance

Table 2a: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy	Other
Mycoplasma	Safety	(b) (4) manufacturing process	(b) (4)	N/A
(b) (4)	Safety	(b) (4) manufacturing process		N/A

Adventitious viruses	Safety	(b) (4) manufacturing process	(b) (4)	N/A
Endotoxin	Safety and purity	Raw materials and manufacturing process		N/A
Bioburden	Safety, purity, and efficacy	Raw materials and manufacturing process		N/A
DNA	Safety	(b) (4) manufacturing process		N/A
Host cell protein	Safety	(b) (4) manufacturing process		N/A
(b) (4)	Safety	(b) (4) manufacturing process		N/A
pH	Efficacy and product stability	Manufacturing process		N/A

- Description: Nivolumab is a human monoclonal immunoglobulin G4 (IgG4) antibody consisting of four polypeptide chains; two identical heavy chains of 440 amino acids and two identical kappa light chains of 214 amino acids, which are linked through inter-chain disulfide bonds. The heavy chain includes S221P mutation which is known to impart increased stability. The calculated molecular weight of nivolumab is 146,221 Da. The nivolumab-(b) (4) (b) (4) (b) (4) drug substance in this BLA.

- Mechanism of Action (MoA): Nivolumab is a PD-1 immune checkpoint inhibitor. 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.

- Potency Assay: Two assays are used in the control of nivolumab- (b) (4), a cell-based assay, and a binding ELISA.
  Cell-Based Bioassay: The cell-based potency assay measures the inhibition of PD-1/PD-L1 by nivolumab, which restores T-cell activation and elicits IL-2 production. The bioassay uses Jurkat E6.1 T-cells that express the human PD-1 receptor, and Raji B-cells that express human PD-L1. Activation of the Jurkat E6.1-huPD-1 T-cell line occurs through interaction of B7.1/B7.2 on the Raji-huPD-L1 cell with CD28 on the Jurkat E6.1-huPD-1 cells and a soluble anti-huCD3-ε monoclonal antibody. CD3/CD28 activation of the Jurkat T cells is inhibited by the interaction of the PD1 receptor on the Jurkat cells with the PD-L1 on the B cells. Nivolumab disrupts PD-1/PD-L1 binding resulting in activation of the Jurkat cells and IL-2 secretion. IL-2 expression is detected using an ELISA assay.
  Binding ELISA: The binding ELISA assay measures the binding of nivolumab to the PD-1 receptor. For the assay, nivolumab is added to plates coated with a recombinant PD-1 receptor/FC chimera. Bound nivolumab is detected with an anti-human IgG4-HRP antibody enzyme conjugate. Binding activity is measured using a TMB substrate, which develops a color in the presence of HRP that can be measured at 450 nm.

- Reference Materials: An in-house reference standard is utilized to support release and stability testing. A two-tier reference standard strategy has been implemented for the nivolumab program. The reference standard for nivolumab- (b) (4)
  (b) (4)

- Critical starting materials or intermediates: (b) (4)
  (b) (4)

- Manufacturing process summary: (b) (4)
  (b) (4)

(b) (4)

- Container closure: The nivolumab (b) (4) drug substance is stored in (b) (4)
- Dating period and storage conditions: See Section I.C above.

ii. Relatlimab drug substance

Table 2b: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy	Other
Mycoplasma	Safety	(b) (4) manufacturing process	(b) (4)	N/A
(b) (4)	Safety	(b) (4) manufacturing process		N/A
Adventitious viruses	Safety	(b) (4) manufacturing process		N/A
Endotoxin	Safety and purity	Raw materials and manufacturing process		N/A
Bioburden	Safety, purity and efficacy	Raw materials and manufacturing process		N/A
DNA	Safety	(b) (4) manufacturing process		N/A

Host cell protein	Safety	(b) (4) manufacturing process	(b) (4)	N/A
(b) (4)	Safety	(b) (4) manufacturing process		N/A
pH	Efficacy and product stability	Manufacturing process		N/A
Appearance	Safety, and efficacy	Manufacturing process, storage		N/A

- Description: Relatlimab is an IgG4 isotype antibody with a S228P mutation within the heavy chain to stabilize the hinge region and prevent antibody arm exchange. Each relatlimab antibody consists of two heavy chains and two light chain each of which has a mass of 23.4 and 50.7 kDa, respectively. The total theoretical mass is 148.2 kDa.

- Mechanism of Action (MoA): Relatlimab binds to LAG-3 to prevent binding of LAG-3 to the major histocompatibility complex (MHC) class II, which is the peptide antigen presentation molecule recognized by CD4+ T cells. By blocking the interaction between LAG-3 on CD4+ cells and MHC class II, relatlimab restores anti-tumor immune response. The mechanism of action does not involve effector function.

- Potency Assay: The potency assay for relatlimab uses an engineered LAG3 expressing T-cell line (3A9) which is co-incubated with an antigen presenting C cell lymphoma MHCII expressing cell line (LK35.2) stimulated with a Hen Egg Lysozyme peptide. In the absence of relatlimab, the interaction between the MHCII/peptide complex on the surface of the LK35.2 cells and the T cell receptor (TCR) on the 3A9 cells is inhibited by human LAG3. Binding of relatlimab to LAG3 restores the interaction between the MHCII/peptide complex with the TCR and IL-2 secretion. IL-2 expression is detected using an ELISA assay.

- Reference Materials: An in-house reference standard is utilized to support release and stability testing of relatlimab. A two-tier reference standard strategy has been implemented for the relatlimab program. (b) (4)
(b) (4)
(b) (4)
(b) (4)

- Critical starting materials or intermediates: (b) (4)

(b) (4)

- Manufacturing process summary: (b) (4)

(b) (4)

- Container closure: The relatlimab drug substance is stored in (b) (4)
- Dating period and storage conditions: See Section I.C above.

C. Drug Product Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. For additional information, see the OPQ primary technical memorandums in Panorama.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Protein Ratio of nivolumab and relatlimab	Dose accuracy	Manufacturing process	(b) (4)	N/A
Particulate Matter	Safety	Manufacturing process, storage		N/A
Sterility (contaminant)	Safety, purity and efficacy	Manufacturing process, failure of		N/A

		container closure integrity	(b) (4)	
Endotoxin (contaminant)	Safety and purity	Raw materials, manufacturing process		The endotoxin detection method is not able to reliably detect endotoxin from the drug product. The Applicant implemented the rabbit pyrogen test as an interim release test and committed to develop a new endotoxin detection method.
Container Closure Integrity (sterility assurance)	Safety and efficacy	Breach during manufacture or storage		N/A
pH	Product stability, efficacy	Formulation		N/A
(b) (4)	Product stability, efficacy	Manufacturing process		N/A
Extractable Volume	Dose accuracy	Manufacturing process		N/A
Appearance	Safety	Manufacturing process, storage		N/A

- Potency and Strength: Opdualag is a fixed dose combination of 240 mg nivolumab and 80 mg relatlimab per 20 mL (12 mg and 4 mg /mL)

- Summary of Product Design: Opdualag is supplied as a 20 mL single-use glass vial.

- List of Excipients: Histidine (1.1 mg/mL), histidine hydrochloride monohydrate (2.7 mg/mL), sucrose (85.6 mg/mL), pentetic acid (0.008 mg/mL), polysorbate 80 (0.5 mg/mL), and Water for Injection.

- Reference Materials: The reference standards (b) (4) (b) (4) (b) (4)
- Manufacturing process summary: The drug product is manufactured (b) (4) (b) (4)
- Container closure: The drug product is packaged in a (b) (4) Type (b) (4) clear tubing glass vial, stoppered with a (b) (4) rubber stopper, and yellow Flip-Off seal. The presentation is packaged in a paperboard folding carton.
- Dating period and storage conditions: see Section I.C
- List of co-package components, if applicable: None

D. Biopharmaceutics Considerations: None

E. Novel Approaches/Precedents: None

F. Any Special Product Quality Labeling Recommendations: None

G. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Bristol-Myers Squibb Company	Relatlimab and nivolumab-(b) (4) Master cell bank storage	FEI: 3008455069	Pre-license inspection required	No observations or FDA Form	Approve – based on inspection

(Devens, MA, USA) *Referred to as BMS-Devens.*	Working cell bank storage Drug substance manufacture Drug substance storage Drug substance quality control testing	DUNS: 860967566		483 issued at the conclusion of the inspection	
Bristol-Myers Squibb Company (East Syracuse, NY, USA) *Referred to as BMS-Syracuse.*	Relatlimab and nivolumab-(b) (4) Master cell bank storage Working cell bank manufacture Working cell bank storage	FEI: 1317757 DUNS: 002230902	No evaluation necessary	N/A	No evaluation necessary
(b) (4)			Facility was found compliant based on file review	N/A	Approve – based on previous history
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			Facility was found compliant based on file review	N/A	Approve – based on previous history
			No evaluation necessary	N/A	No evaluation necessary

(b) (4)					
DRUG PRODUCT					
(b) (4)			Facility was found compliant based on file review	N/A	Approve – based on waiver granted by OPMA/OBP
			Facility was found compliant based on file review	N/A	Approve – based on previous history
			Facility was found compliant based on file review	N/A	Approve – based on previous history
Bristol-Myers Squibb Company One Squibb Drive New Brunswick, New Jersey 08903-0191 USA	Drug product release	FEI: 2211101 DUNS: 011550092	No evaluation necessary	N/A	No evaluation necessary
(b) (4)			Facility was found compliant	N/A	Approve – based on previous history

			based on file review		

H. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Bristol Myers Squibb Company (FEI 3008455069), proposed for relatlimab and nivolumab-(b) (4) drug substance manufacture. A pre-license inspection was conducted from October 13-20, 2021 in support of BLA 761234 for relatlimab and nivolumab-(b) (4) drug substances. The inspection concluded with no FDA Form-483 issued and a recommendation of approve for BLA 761234 (CMS WA 416767).
Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) proposed for drug product manufacture. Based on the site's history, the inspection of the drug product manufacturing site was waived. Refer to the waiver memorandum in Panorama.
All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.
For additional information, see the OPQ Facilities memorandum in Panorama.

I. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:

Relatlimab

(b) (4)

- Drug substance stability protocol for registrational and PPQ batches
- Post-approval annual stability protocol

Nivolumab-(b) (4)

(b) (4)

- Drug substance stability protocol for registrational and PPQ batches
- Post-approval annual stability protocol

ii. Outstanding assessment issues/residual risk: PMC for re-evaluation of acceptance criteria for potency of relatlimab drug substance

iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
- Drug product stability protocol for PPQ batches
- Post-approval annual stability protocol
- Inorganic leachables study results
- Commercial shipping qualification protocol

ii. Outstanding assessment issues/residual risk: PMCs for re-evaluation of acceptance criteria for potency of relatlimab in the drug product and to develop an endotoxin release method for the drug product which mitigates the low endotoxin recovery (LER) effect.

iii. Future inspection points to consider: None

Anjali Shukla

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Patrick Lynch

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Date: 1/19/2022 03:20:58PM
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/s/

ANIKA A LALMANSINGH
01/19/2022 04:10:50 PM

ANJALI A SHUKLA
01/19/2022 04:12:37 PM