

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761169Orig1s000

PRODUCT QUALITY REVIEW(S)

First Approval for Indication/Breakthrough Review/Priority Review

Recommendation: Approval

BLA Number: 761169
Review Date: September 30, 2020
Addendum

Drug Name/Dosage Form	Inmazed (atoltivimab, maftivimab, odesivimab-ebgn) injection
Strength/Potency	241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)
Route of Administration	intravenous
Rx/OTC dispensed	Rx
Indication	for the treatment of infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for <i>Zaire ebolavirus</i> infection
Applicant	Regeneron Pharmaceuticals, Inc.

Product Overview:

Inmazed (atoltivimab, maftivimab, odesivimab-ebgn) is a combination of 3 recombinant human IgG1, κ monoclonal antibodies (mAb) directed against the Ebola Virus surface glycoprotein (EBOV GP). Each mAb in the cocktail binds with high affinity to different, non-overlapping or potentially partially-overlapping regions on the EBOV GP. Odesivimab also binds to soluble EBOV GP. Maftivimab and atoltivimab neutralize virus entry in an in vitro assay using Viral Like Particles (VLPs). Atoltivimab and odesivimab bind FcγRIIIa and kill EBOV GP expressing cells by antibody-dependent cellular cytotoxicity (ADCC).

Each individual mAb drug substance (DS) is produced in Chinese Hamster Ovary (CHO) cells engineered (b) (4) Atoltivimab, maftivimab, odesivimab-ebgn drug product (DP) is supplied at 241.7 mg of altotivimab, 241.7 mg of maftivimab, and 241.7 mg of odesivimab per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL) per vial. Atoltivimab, maftivimab, odesivimab-ebgn is indicated in adult and pediatric patients for the treatment of infection caused by *Zaire ebolavirus*.

Quality Review Team:

Discipline	Reviewer	Branch/Division
Drug Substance	Tzanko Stantchev and Milos Dokmanovic	OBP/DBRR1
Drug Product	Tzanko Stantchev and Jens Fricke	OBP/DBRR1
Immunogenicity	Milos Dokmanovic	OBP/DBRR1
Labeling	Vicky Borders-Hemphill	OBP/IO
Facility	Kathleen Jones/Thuy Nguyen (TL)	OPMA/DBM/BMB1
Microbiology DS	Reyes Candau-Chacon DS/Patricia Hughes (TL)	OPMA/DBM/ BMB2
Microbiology DP	Bo Chi/Candace Gomez-Broughton (TL)	OPMA/DBM/BMB1
Application Team Lead	Marjorie Shapiro	OBP/DBRR1
OBP Tertiary Reviewer	Qing (Joanna) Zhou	OBP/DBRR1
RBPM	Marquita Burnett/Anh-Thy Ly	OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Alicia Moruf	OND/ORO/DROID
Cross-disciplinary Team Lead	Kim Struble	OND/OAP/DAVP
Medical Officer	Ben Lorenz	OND/OAP/DAVP
Pharmacology/Toxicology	John Dubinion/Chris Ellis TL	OND/OID/DPTID
Clinical Virology	Eric Donaldson/Jules O'Rear TL	OND/OAP/DAVP
Clinical Pharmacology	Mario Sampson/ Su Young Choi TL	OTS/OCP/DIDP

Statistics	Wen Zeng/ Thamban Valappil TL	OTS/OB/DBIV

1. Names:

- a. Proprietary Name: Inmazedb
- b. Trade Name: Inmazedb
- c. Non-Proprietary Name: atoltivimab, maftivimab, odesivimab-ebgn
- d. USAN/INN name: atoltivimab, maftivimab, odesivimab
- e. CAS Name: REGN3470 -21 35632-29-8; REGN3471 -21 35632-30-1; REGN3479 - 21 35632-36-7
- f. Common Name: REGN3470 (atoltivimab); REGN3471 (odesivimab); REGN3479 (maftivimab)
- g. Compendial Name: none
- h. OBP systematic name: MAB HUMAN (IGG1) ANTI-X5HMX4 (X5HMX4_9MONO)[REGN3470]; MAB HUMAN (IGG1) ANTI-X5HMX4 (X5HMX4_9MONO) [REGN3471]; MAB HUMAN (IGG1) ANTI-X5HMX4 (X5HMX4_9MONO)[REGN3479]

Purpose of Addendum: Ongoing labeling discussions since the primary reviews were due led to additional information requests and responses from Regeneron. These include:

- 1. The approved indication will include the treatment of neonates. 5% Dextrose is used as the diluent for neonates. A PMC was added for an in-use study using 5% Dextrose as a diluent.
- 2. Final details of the request for an exception to labeling requirements for the vial were submitted. See updates to item 9 under Novel Approaches.

3.  (b) (4)

Submissions Reviewed Since 9/8/2020:

Submission(s) Reviewed	Document Date
BLA 761169.56 Response to 9/4/2020 IR for request for an exception to labeling requirements for the vial	9/11/2020
BLA 761169.57 Container and carton labeling strength presentation	9/11/2020
BLA 761169.58 Response to 9/11 PMC IR; acceptance of in-use study PMC	9/15/2020
BLA 761169.59 Response to 9/15/2020 IR for request for an exception to labeling requirements for the vial	9/18/2020
BLA 761169.62 Response to 9/17/202 IR PMC IR; agreement for submission time frame for in-use study PMC	9/18/2020
BLA 761169.64 Request for an exception to labeling requirements for the vial	9/23/2020
BLA 761169.65 Container and carton labeling strength presentation	9/25/2020
BLA 761169.67 Container and carton labeling and PI	10/2/2020

Executive Summary Addendum:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Biotechnology Products and the Office of Pharmaceutical Manufacturing Assessment, OPQ, CDER, recommend approval of STN 761169 for Inmazeb manufactured by Regeneron Pharmaceuticals, Inc. The data submitted in this application and its amendments are adequate to support the conclusion that the manufacture of Inmazeb is well-controlled, provides assurance of sterility 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: Regeneron Pharmaceuticals, Inc. Rensselaer, NY USA
 - Drug Product: [REDACTED] (b) (4)
- Fill size and dosage form
 - 241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)
 - injection
- Dating period:
 - Drug Product: 30 months: 2-8°C
 - Drug Substance: [REDACTED] (b) (4)
 - 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 substance and drug product under 21 CFR 601.12.
- Exempt from lot release:
 - Yes: Inmazeb is a specified product exempt from lot release per 21 CFR 601.2a.

C. Benefit/Risk Considerations:

Inmazeb (atoltivimab, maftivimab, odesivimab -ebgn) is indicated for the treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for *Zaire ebolavirus* infection. It is a combination of three monoclonal antibodies directed against non-overlapping epitopes of the *Zaire ebolavirus* surface glycoprotein. The proposed dosing regimen is 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg (3 mL/kg) diluted and administered as a single intravenous infusion.

It was designated as a Breakthrough Therapy on 9/3/2019 and granted Orphan Drug Status on 12/23/2019 for post-exposure prophylaxis under IND 125507. It was studied in the PAMoja TuLinde Maisha (PALM) randomized controlled trial sponsored by NIAID under IND 125530 and supported by non-clinical studies [REDACTED] (b) (4). After preliminary results of the PALM study showed superiority of atoltivimab, maftivimab, odesivimab-ebgn in Ebola infected patients in August 2019, a series of meetings, including two CMC-only meetings, were held to discuss a path to expedite licensure.

This BLA contains several precedents, most notably, the first approval of a monoclonal antibody cocktail. The precedents are further described in Section 2D.

The overall control strategy for atoltivimab, maftivimab, odesivimab-ebgn manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, release of drug substance and drug product, and stability of these materials. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The drug product manufacturing process provides sterility assurance and microbiology product quality. The currently proposed control strategies ensure process consistency.

The technical assessments for product quality and immunogenicity assays (OBP), microbiological product quality and facility (OPMA), and OBP labeling are located as separate documents in Panorama.

<https://panorama.fda.gov/search?objCode=DOCU&allowRedirect=false&query=761169&showResultsPage=true>

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

- 3936-7. Re-evaluate and update REGN-EB3 drug substance (DS) and drug product lot release and stability specifications based on lots manufactured by the (b) (4) DS processes. The corresponding data, the analysis and updated specifications will be submitted with the PAS for the registration of the (b) (4) commercial manufacturing process.

Final Report Submission: 01/2021

- 3936-8. Conduct a real-world Transport Qualification study that includes a product quality assessment using REGN-EB3 drug product. The real-world Transport Qualification study results will be submitted in a final report to the BLA.

Final Report Submission: 08/2021

- 3936-9. Re-evaluate and optimize the manufacture, qualification and stability controls used to ensure the performance of Ebola Virus- Like Particles (VLPs) in the Pseudovirus neutralization assays. The re-evaluation, development study results and the final control strategy for Ebola VLPs will be provided in the final report to the BLA.

Final Report Submission: 12/2021

- 3936-10. Provide microbial hold time data in a microbial challenge study to support the total in-use time (storage and infusion time) of diluted INMAZEB in 5 % Dextrose Injection beyond 4-hours at ambient temperature. The study should be conducted for twice the worst-case in-use time and bracketing the drug product concentrations that would be administered to patients. The study should also be representative of the in-use conditions; for example, neonates may be kept at temperatures above 20-25°C during infusion and the higher temperatures should be simulated in the study supporting in-use conditions

Final Report Submission: 4/2021 (PAS)

II. Summary of Quality Assessments:

Novel Approaches/Precedents:

1. This is the first approval of a mAb cocktail, which is considered a fixed dose combination product.
2. A BLA was initially planned for submission in 2022; however, due to the early readout of the clinical study in the Democratic Republic of Congo showing efficacy of REGN-EB3, plans for submission of a BLA were expedited. Because of the urgent need for the product, Regeneron submitted the BLA describing the clinical manufacturing process rather than the proposed commercial process. The proposed commercial process will be submitted as a PAS subsequent to approval of the BLA.
3.  (b) (4)
4. 
5. 
6. 
7. Labeling:
 - a. The mAbs are listed in alphabetical order on the carton and container labels and in the Prescribing information
 - b. There is only one suffix attached to the final mAb in the list.
 - c. Strength is presented to specify the amount of each active ingredient "241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)" on the carton and container label.
 - d. In the Prescribing information, strength is presented to specify the amount of each active ingredient "241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)" in the following Sections Highlights Dosage Forms and Strengths; Section 3 Dosage Forms and Strengths; Section 11 Description; and Section 16 How Supplied/Storage and Handling.
8. At the recommended dose of 150 mg/kg/2hr, the potential endotoxin input for the proposed worst-case of (b) (4) mg/mL product concentration during infusion could be (b) (4) EU/kg/hr in a patient weighing 80 kg. This includes endotoxin input from both Inmazeb and the infusion solution ((b) (4) EU/mL USP endotoxin limit). To ensure that the USP endotoxin safety limit of (b) (4) (b) (4) will be maintained, Section 2.2 Preparation and Administration in the Prescribing Information includes a table showing infusion volumes and times by body weight and the worst-case product concentration during infusion was changed to 9.5 mg/mL.
9. In IR#12, dated July 27, 2020, the Agency requested that Regeneron submit an exception for labeling requirements to include the expiration date on the REGN-EB3 vial label to avoid the necessity to submit a request and a relabeling protocol post-marketing. Per 21 CFR 610.68 "A Strategic National Stockpile official or any entity that manufactures (including labeling, packing, relabeling, or repackaging), distributes, or stores a biological product that is or will be included in the Strategic National Stockpile may submit, with written concurrence from a

Strategic National Stockpile official, a written request for an exception or alternative described in paragraph (a) of this section to the Center Director.” The exception in 21 CFR610.68 does not include the carton. During the Late Cycle Meeting on August 31, 2020, Regeneron confirmed that they were working with BARDA and the SNS to submit this request for the vial. The request is likely to be granted; see the action letter for the final decision made regarding this request.

(b) (4)

(b) (4)

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

/s/

MARJORIE A SHAPIRO
10/06/2020 02:16:56 PM

QING ZHOU
10/06/2020 02:28:24 PM



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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	October 6, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Jens Fricke, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761169
Applicant:	Regeneron Pharmaceuticals, Inc.
Submission Date:	February 25, 2020
Product:	atoltivimab, maftivimab, and odesivimab-ebgn
Dosage form(s):	injection
Strength and Container-Closure:	241.7 mg of atoltivimab, 241.7 mg of maftivimab, and 241.7 mg of odesivimab per 14.5 mL (16.67 mg/16.67 mg/16.67 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, container labels, and carton labeling submitted on October 2, 2020 are acceptable 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, container labels, and carton labeling submitted on October 2, 2020 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

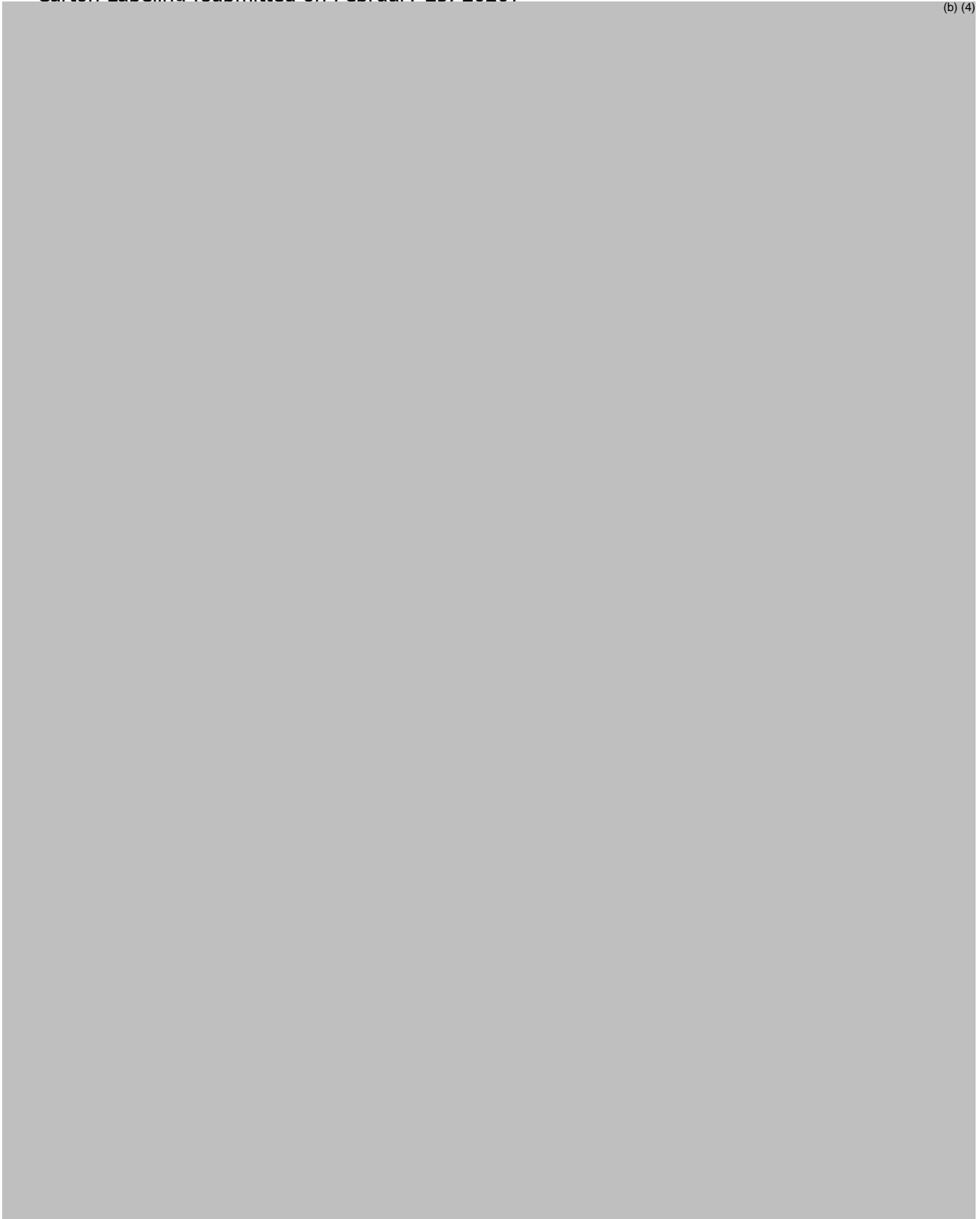
Appendix A: Proposed Labeling

Prescribing Information (submitted on February 25, 2020

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Container Labels (submitted on February 25, 2020)





Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ 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
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that the proper names are revised to appear in alphabetical order throughout all labels and labeling for consistency.
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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label⁵)</i>	☒ Yes ☐ No ☐ N/A

¹ Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

² Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

³ Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

⁴ Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

⁵ Per 21 CFR 610.60(c) *Partial Label*. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

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 ☐ N/A

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

Comment/Recommendation: *See SNS exception request*

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

Comment/Recommendation: (b) (4)

The Applicant revised as requested

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

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

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

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

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

Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials.
Applicant's response: The Sponsor confirms there is no text on the ferrule and cap overseal of the vials.

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

Comment/Recommendation: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.
Applicant's response: The Sponsor confirms that the vial label dimensions and placement on the vial were developed to permit unobstructed visibility of the product following application of the label on the vial. The area of visual inspection is located along the full length of the vial where the leading edge and trailing edge of the label leave an unobstructed area to view the vial contents.

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

Package type term (container label)	Acceptable
<i>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</i>	☒ 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
<i>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), which, when finalized, will represent FDA's current thinking on topic</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that a linear barcode appears on the container label
Applicant's response: The Sponsor acknowledges the Agency's comment and added a linear barcode in a vertical position on the label.

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

Comment/Recommendation: *The Applicant requested an expiration date exemption for the vial label (b) (4) intends an expiration date on pallets with paper and online dear healthcare provider letter that provides expiration dates of exempted lots.*

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>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).</i>	☒ Yes ☐ No ☐ N/A

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

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No ☒ N/A

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

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

Package⁶ 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
<i>Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that the proper names are revised to appear in alphabetical order throughout all labels and labeling for consistency.
The Applicant revised as requested

Manufacturer name, address, and license number (package labeling)	Acceptable
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ 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

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.

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

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

Comment/Recommendation: (b) (4)
<i>The Applicant revised as requested</i>

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

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

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

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i>	☒ 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
<i>Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider revising the presentation of the inactive ingredients to have the quantitative amounts of the active ingredients appear in front of the name and the quantitative amounts of the inactive ingredients appear in after the name in parenthesis to differentiate the actives from inactives. The inactive ingredients have been revised to appear in alphabetical order:

"Each vial contains 241.7 mg of atoltivimab, 241.7 mg of maftivimab, and 241.7 mg of odesivimab in 14.5 mL. Each mL contains 16.67 mg of atoltivimab, 16.67 mg of maftivimab, 16.67 mg of odesivimab, and L-histidine (0.74 mg), L-histidine monohydrochloride monohydrate (1.09 mg), polysorbate 80 (1 mg), sucrose (100 mg), and Water for Injection, USP with a pH of 6.0."

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
<i>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</i>	☒ 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: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>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)</i>	☒ 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

Comment/Recommendation: *The Applicant requested an expiration date exemption for the vial label (b) (4) intends an expiration date on pallets with paper and online dear healthcare provider letter that provides expiration dates of exempted lots.*

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
<i>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</i>	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	Acceptable
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ 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
<i>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</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ 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: Consider revising the statement of dosage from [REDACTED] (b) (4) to read as follows: "Dosage: See Prescribing Information" <i>The Applicant revised per DMEPA request "Dosage and Administration: See Prescribing Information"</i>

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Ensure that the proper names are revised to appear in alphabetical order throughout all labels and labeling for consistency.
The Applicant revised as requested

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

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

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv)] <i>Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted drug; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes); confirm product's incompatibilities, and 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.</i>	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the storage requirements in table 2 for clarity and included "refrigerated" in each column and "for no more than 4 hours" for storage conditions for D5W and LR. *The Applicant revised as requested*
Added the storage time ("for no more than 4 hours or refrigerated..") for clarity for the room temperature storage for product diluted in D5W or LR, please confirm. *The Applicant accepted and confirmed*
The visually inspect statement has been revised to the verbatim language per 21 CFR 201.57(c)(3)(iv). *The Applicant revised as requested*
Consider deletion of the analytical test terminology (b) (4) as it may present the healthcare provider with ambiguity when deciding to discard the product due to visible particles. *The Applicant revised to "that is free from visible particulates". Acceptable*
Note: The dose is (b) (4) 50 mg of atolivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg of body weight; dose is calculated based on infusion volume per patient weight in kg (3 mL/kg of (b) (4) 4.5 mL solution) using table in the prescribing information that provides the infusion volumes and infusion times per body weight to facilitate ease of dose calculation

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: [REDACTED] (b) (4)
 [REDACTED] *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
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Deleted [REDACTED] (b) (4)
 [REDACTED]
The Applicant revised as requested

[REDACTED] (b) (4)
 [REDACTED]
 [REDACTED]
 [REDACTED]
The Applicant revised as requested

Full Prescribing Information	
15 & 16 Cytotoxic 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 cytotoxic 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
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation:	(b) (4)
 <i>The Applicant</i>	
<i>revised as requested</i>	

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

Medication Guide Evaluation (N/A)
 Patient Information Labeling Evaluation (N/A)
 Instructions for Use Evaluation (N/A)

APPENDIX C. Acceptable Labels and Labeling

Prescribing Information (submitted on October 2, 2020
<\\CDSESUB1\evsprod\bla761169\0067\m1\us\114-labeling\114a-draft-label\proposed.pdf>)

Container Labels (submitted on October 2, 2020)



(b) (4)





Vicky
Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 10/06/2020 01:23:48PM
GUID: 50814c7000007a3d59329f660d8ddf02



Jens
Fricke

Digitally signed by Jens Fricke
Date: 10/06/2020 01:36:25PM
GUID: 57d6a75701b1361db26ba4f78c02a5a9

First Approval for Indication/Breakthrough Review/Priority Review

Recommendation: Approval

BLA Number: 761169
Review Date: September 8, 2020

Drug Name/Dosage Form	Inmazed (atoltivimab, maftivimab, odesivimab-ebgn) injection
Strength/Potency	241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)
Route of Administration	intravenous
Rx/OTC dispensed	Rx
Indication	for the treatment of infection caused by Zaire ebolavirus in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for <i>Zaire ebolavirus</i> infection
Applicant	Regeneron Pharmaceuticals, Inc.

Product Overview:

Inmazed (atoltivimab, maftivimab, odesivimab-ebgn) is a combination of 3 recombinant human IgG1, κ monoclonal antibodies (mAb) directed against the Ebola Virus surface glycoprotein (EBOV GP). Each mAb in the cocktail binds with high affinity to different, non-overlapping or potentially partially-overlapping regions on the EBOV GP. Odesivimab also binds to soluble EBOV GP. Maftivimab and atoltivimab neutralize virus entry in an in vitro assay using Viral Like Particles (VLPs). Atoltivimab and odesivimab bind FcγRIIIa and kill EBOV GP expressing cells by antibody-dependent cellular cytotoxicity (ADCC).

Each individual mAb drug substance (DS) is produced in Chinese Hamster Ovary (CHO) cells engineered (b) (4). Atoltivimab, maftivimab, odesivimab-ebgn drug product (DP) is supplied at 241.7 mg of altotivimab, 241.7 mg of maftivimab, and 241.7 mg of odesivimab per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL) per vial. Atoltivimab, maftivimab, odesivimab-ebgn is indicated in adult and pediatric patients for the treatment of infection caused by *Zaire ebolavirus*.

Quality Review Team:

Discipline	Reviewer	Branch/Division
Drug Substance	Tzanko Stantchev and Milos Dokmanovic	OBP/DBRR1
Drug Product	Tzanko Stantchev and Jens Fricke	OBP/DBRR1
Immunogenicity	Milos Dokmanovic	OBP/DBRR1
Labeling	Vicky Borders-Hemphill	OBP/IO
Facility	Kathleen Jones/Thuy Nguyen (TL)	OPMA/DBM/BMB1
Microbiology DS	Reyes Candau-Chacon DS/Patricia Hughes (TL)	OPMA/DBM/ BMB2
Microbiology DP	Bo Chi/Candace Gomez-Broughton (TL)	OPMA/DBM/BMB1
Application Team Lead	Marjorie Shapiro	OBP/DBRR1
OBP Tertiary Reviewer	Qing (Joanna) Zhou	OBP/DBRR1
RBPM	Marquita Burnett/Anh-Thy Ly	OPRO

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Alicia Moruf	OND/ORO/DROID
Cross-disciplinary Team Lead	Kim Struble	OND/OAP/DAVP
Medical Officer	Ben Lorenz	OND/OAP/DAVP
Pharmacology/Toxicology	John Dubinion/Chris Ellis TL	OND/OID/DPTID
Clinical Virology	Eric Donaldson/Jules O'Rear TL	OND/OAP/DAVP
Clinical Pharmacology	Mario Sampson/ Su Young Choi TL	OTS/OCP/DIDP
Statistics	Wen Zeng/ Thamban Valappil TL	OTS/OB/DBIV

1. Names:

- a. Proprietary Name: Inmazedb
- b. Trade Name: Inmazedb
- c. Non-Proprietary Name: atoltivimab, maftivimab, odesivimab-ebgn
- d. USAN/INN name: atoltivimab, maftivimab, odesivimab
- e. CAS Name: REGN3470 -21 35632-29-8; REGN3471 -21 35632-30-1; REGN3479 - 21 35632-36-7
- f. Common Name: REGN3470 (atoltivimab); REGN3471 (odesivimab); REGN3479 (maftivimab)
- g. Compendial Name: none
- h. OBP systematic name: MAB HUMAN (IGG1) ANTI-X5HMX4 (X5HMX4_9MONO)[REGN3470]; MAB HUMAN (IGG1) ANTI-X5HMX4 (X5HMX4_9MONO) [REGN3471]; MAB HUMAN (IGG1) ANTI-X5HMX4 (X5HMX4_9MONO)[REGN3479]

Submissions Reviewed:

Submission(s) Reviewed	Document Date
BLA 761169.0001 DS PPQ validation Protocol	10/4/2019
BLA 761169.0002 DS and DP except PPQ lots	12/23/2019
BLA 761169.0003 Updated DP sections and DS methods	1/31/2020
BLA 761169.0005 response to IR#1 (2/14/20) DS and DP Micro	2/25/2020
BLA 761169.0012 partial response to IR #2 (3/13/20) DS Micro, DS and DP	3/30/2020
BLA 761169.0014 DP PPQ lots	3/31/2020
BLA 761169.0016 remaining response to IR #2 (3/13/20)	4/7/2020
BLA 761169.0018 response to IR #3 (4/3/2020) DP, LOA, labeling	4/17/2020
BLA 761169.0021 response to IR #4 (4/30/20) DS and DP	5/15/2020
BLA 761169.0022 response to IR #5 (5/7/20) DP Micro	5/20/2020
BLA 761169.0023 response to IR #4 (4/30/20) DS and DP	5/21/2020
BLA 761169.0024 response to IR #6 (5/18/20) DP Micro	5/27/2020
BLA 761169.0025 response to IR #7 (5/22/20) DP Micro	5/29/2020
BLA 761169.0027 response to IR from DAV regarding volume infused and endotoxin levels due to diluent	6/2/2020
BLA 761169.30 response to IR #8 (6/15/20) (ADA)	6/23/2020
BLA 761169.31 response to IR #7 (5/22/2020) (b) (4) validation protocol	6/24/2020
BLA 761169.32 response to IR #5 (5/7/20) DP PPQ lots 2 and 3	7/1/2020
BLA 761169.37 response to IR #9 (7/7/20) DP Micro	7/17/2020
BLA 761169.40 response to IR #10 (7/13) DS and #11 (7/17/20) DP micro	7/24/2020
BLA 761169.41 response to IR #12 (7/27/20) DP and labeling	8/3/2020
BLA 761169.44 (b) (4) validation study	8/7/2020
BLA 761169.45 response to IR #11 (7/17/20) DP micro	8/17/2020
BLA 761169.46 response to IR #13 (7/17/20) DP micro (follow up for (b) (4) validation study	8/18/2020
BLA 761169.50 agreement to proposed PMRs/PMCs, including CMC PMCs 5 (specifications) and 6 (real world transport shipping	8/26/2020
BLA 761169.52 response to carton and vial labeling IR (8/21/2020)	8/28/2020
BLA 761169.53 agreement to PMC for optimization of VLPs	8/28/2020
BLA 761169.54 Response to IR#14 DP micro and update to Table 5 S.5.	9/4/2020

Communications Other than IRs:

Submission(s) Reviewed	Document Date
Mid-cycle communication	6/6/2020
Mid-cycle meeting	6/8/2020
Teleconference to discuss potential PMCs and (b) (4) PAS	8/4/2020
Late-cycle communication	8/21/2020
Late-cycle meeting	8/31/2020

Quality Review 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	Comments
(b) (4)	V	(b) (4)	(b) (4)	3	Adequate	
	III			2	Adequate	
	III			3	Adequate	
	III			3	Adequate	
	V			2	Adequate	
	V			2	Adequate	

1. Action codes for DMF Table: 1- DMF Reviewed; Other codes indicate why the DMF was not reviewed, as follows: 2- Reviewed previously and no revision since last review; 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 not enough data in the application; therefore, the DMF did not need to be reviewed).

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application: none

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:

Regeneron claims a categorical exclusion from the requirement to prepare an environmental assessment under 21CFR Part 25, Subpart C, Categorical Exclusions, Section 25.31(c); furthermore, no extraordinary circumstances exist per 21 CFR Section 25.21 that would warrant preparation of such an assessment. The claim of categorical exemption is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Biotechnology Products and the Office of Pharmaceutical Manufacturing Assessment, OPQ, CDER, recommend approval of STN 761169 for Inmazeb manufactured by Regeneron Pharmaceuticals, Inc. The data submitted in this application and its amendments are adequate to support the conclusion that the manufacture of Inmazeb is well-controlled, provides assurance of sterility 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: Regeneron Pharmaceuticals, Inc. Rensselaer, NY USA
 - Drug Product: (b) (4)

- Fill size and dosage form
 - 241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)
 - injection

- Dating period:
 - Drug Product: 30 months: 2-8°C
 - Drug Substance: (b) (4) months: (b) (4) °C
 - 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 substance and drug product under 21 CFR 601.12.

- Exempt from lot release:
 - Yes: Inmazeb is a specified product exempt from lot release per 21 CFR 601.2a.

C. Benefit/Risk Considerations:

Inmazeb (atoltivimab, maftivimab, odesivimab -ebgn) is indicated for the treatment of infection caused by *Zaire ebolavirus* in adult and pediatric patients, including neonates born to a mother who is RT-PCR positive for *Zaire ebolavirus* infection. It is a combination of three monoclonal antibodies directed against non-overlapping epitopes of the *Zaire ebolavirus* surface glycoprotein. The proposed dosing regimen is 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg (3 mL/kg) diluted and administered as a single intravenous infusion.

It was designated as a Breakthrough Therapy on 9/3/2019 and granted Orphan Drug Status on 12/23/2019 for post-exposure prophylaxis under IND 125507. It was studied in the PAMoja TuLinde Maisha (PALM) randomized controlled trial sponsored by NIAID under IND 125530 and supported by non-clinical studies (b) (4). After preliminary results of the PALM study showed superiority of atoltivimab, maftivimab, odesivimab-ebgn in Ebola infected patients in

August 2019, a series of meetings, including two CMC-only meetings, were held to discuss a path to expedite licensure.

This BLA contains several precedents, most notably, the first approval of a monoclonal antibody cocktail. The precedents are further described in Section 2D.

The overall control strategy for atoltivimab, maftivimab, odesivimab-ebgn manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, adventitious agents, release of drug substance and drug product, and stability of these materials. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The drug product manufacturing process provides sterility assurance and microbiology product quality. The currently proposed control strategies ensure process consistency.

The technical assessments for product quality and immunogenicity assays (OBP), microbiological product quality and facility (OPMA), and OBP labeling are located as separate documents in Panorama.

<https://panorama.fda.gov/search?objCode=DOCU&allowRedirect=false&query=761169&showResultsPage=true>

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

5. Re-evaluate and update REGN-EB3 drug substance (DS) and drug product lot release and stability specifications based on lots manufactured by the (b) (4) DS processes. The corresponding data, the analysis and updated specifications will be submitted with the PAS for the registration of the (b) (4) commercial manufacturing process.

Final Report Submission: 01/2021

6. Conduct a real-world Transport Qualification study that includes a product quality assessment using REGN-EB3 drug product. The real-world Transport Qualification study results will be submitted in a final report to the BLA.

Final Report Submission: 08/2021

7. Re-evaluate and optimize the manufacture, qualification and stability controls used to ensure the performance of Ebola Virus- Like Particles (VLPs) in the Pseudovirus neutralization assays. The re-evaluation, development study results and the final control strategy for Ebola VLPs will be provided in the final report to the BLA.

Final Report Submission: 12/2021

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Product development of atoltivimab, maftivimab, and odesivimab was abbreviated due to the positive results in the PAmoja TuLinde Maisha (PALM) randomized controlled trial and the urgent need to make

effective treatments for Ebola virus infections available. Therefore, the identification of CQAs and risk assessments are not fully formed based on specific product knowledge and rely to some degree on Regeneron’s prior knowledge and experience with their platform manufacturing processes.

Tables 1 and 2 summarize the critical quality attributes and the control strategy for each mAb that are relevant to the API and Drug Substance, respectively.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Aggregate (Dimer) (Product Variant) atoltivimab (REGN3470) odesivimab (REGN3471) maftivimab (REGN3479)	Impact on biological activity, immunogenicity, PK/PD, and safety Process	DS manufacturing,		(b) (4)
Fragmentation (Product impurity) atoltivimab (REGN3470) odesivimab (REGN3471) maftivimab (REGN3479)	Impact on biological activity, immunogenicity, PK/PD, and safety	DS manufacturing		
EBOV Neutralization (Potency) atoltivimab (REGN3470) maftivimab (REGN3479)	MOA - Impact on efficacy	Intrinsic to the molecule (b) (4)		
ADCC (Potency) atoltivimab (REGN3470) odesivimab (REGN3471)	MOA - Impact on efficacy	Intrinsic to the molecule (b) (4)		
Identity atoltivimab (REGN3470) odesivimab (REGN3471) maftivimab (REGN3479)	Impact on safety and efficacy	Intrinsic to each mAb		
Charge Variants atoltivimab (REGN3470) odesivimab (REGN3471) maftivimab (REGN3479) REGN-EB3	Impact on biological activity, immunogenicity, PK/PD, and safety	DS manufacturing		

	Process		(b) (4)
Oxidation (Product variant) maftivimab (REGN3479)	Potential impact on biological activity and PK/PD	DS manufacturing	
Non-glycosylated H chain (Product variant) atoltivimab (REGN3470) odesivimab (REGN3471) maftivimab (REGN3479)	Potential impact on biological activity and PK/PD	DS manufacturing	
(b) (4)	Potential impact on biological activity and PK/PD	(b) (4)	

B. Drug Substance Atoltivimab, maftivimab, and odesivimab Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

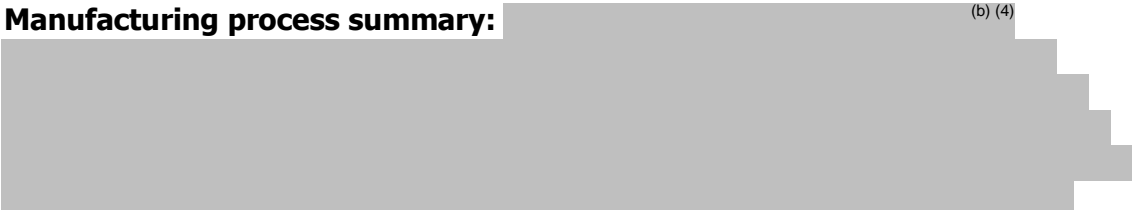
Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management. (Applicable to each mAb)

CQA (type)	Risk	Origin	Control Strategy	Other	
Visual Appearance: color and opalescence (General)	Impact on safety and immunogenicity	DS manufacturing	(b) (4)		
pH (general)	Impact on product stability and conformation	DS manufacturing			
(b) (4)	Impact on product stability and conformation	DS manufacturing			
Osmolality (General)	Potential impact on therapeutic dose	Osmolality (General)			
Protein Quantity (General)	Impact on efficacy	DS manufacturing			
Primary Sequence	Impact on efficacy, safety and immunogenicity	Expression construct and cell line for each mAb			Characterization and comparability methods

			(b) (4)	
Secondary and Tertiary Structure	Impact on efficacy, PK/PD and immunogenicity	Expression construct and cell line for each mAb		Characterization and comparability methods
Glycosylation	Impact on biological activity, PK/PD and immunogenicity	DS manufacturing		(b) (4)
Mannose	Impact on biological activity and PK/PD	DS manufacturing		
Host Cell Proteins (Process Impurity)	Impact on safety and immunogenicity		(b) (4)	
DNA (Process Impurity)	Impact on safety and immunogenicity		(b) (4)	
(Process Impurity)	Impact on safety and immunogenicity		(b) (4)	Toxicological risk assessment provided
(Process Impurity)	Impact on safety		(b) (4)	Toxicological risk assessment provided
(Process Impurity)	Impact on safety		(b) (4)	Toxicological risk assessment provided
(Process Impurity)	Impact on safety		(b) (4)	Toxicological risk assessment provided
(Process Impurity)	Impact on safety, immunogenicity, and allergenicity		(b) (4)	Toxicological risk assessment provided
(Process Impurity)	Impact on safety		(b) (4)	Toxicological risk assessment provided
(Process Impurity)	Impact on safety		(b) (4)	Toxicological risk assessment provided
Endotoxin (Contaminant)	Impact on safety, and immunogenicity	Raw materials or contamination during manufacturing		
Bioburden (Contaminant)	Impact on safety; product quality due to degradation or modification of product	Raw materials or contamination during manufacturing		(b) (4)

- **Description:** Atoltivimab (REGN3470), maftivimab (REGN3479), and odesivimab (REGN3471) are human IgG1, kappa anti-Ebola Virus glycoprotein monoclonal antibodies produced in a CHO cell line engineered (b) (4). The molecular weights are: atoltivimab 144,810.0 Da, maftivimab 145,910.5 Da; and odesivimab 143,695.5 Da. Each mAb has the typical structure of an IgG1 antibody with 4 interchain disulfide bonds and 12 intrachain disulfide bonds.
- **Mechanism of Action (MoA):** Atoltivimab has both ADCC activity and virus neutralization in an in vitro assay using VLPs; maftivimab has virus neutralization activity, and odesivimab has ADCC activity.
- **Potency Assay:**
 - The ability of atoltivimab and maftivimab to block virus entry is assessed in a Pseudovirus Neutralization Assay. Viral like particles (VLPs) encoding the luciferase reporter gene are pseudotyped with EBOV GP (Zaire 2014 strain), incubated with serial dilutions of the mAbs, and subsequently incubated with an Ebola virus susceptible cell line. The level of VLP cellular entry is measured based on luciferase reporter gene activity and reported as a percentage of the reference standard for each mAb.
 - ADCC activity of atoltivimab and odesivimab is assessed using Ebola GP-expressing target HEK293 cells and an Fc γ RIIIa/F176V luciferase-engineered Jurkat cell line. Serial dilutions of each mAb are incubated with the Ebola GP expressing cells, followed by incubation with the Jurkat reporter cells. Upon binding to Ebola GP and Fc γ RIIIa, luciferase is expressed. Activity is reported as a percentage of reference standard for each mAb.
- **Reference Materials:** (b) (4)

- **Critical starting materials or intermediates: Master Cell Banks**
 - (b) (4)

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




(b) (4)

- **Container closure:** [Redacted] (b) (4)
- **Dating period and storage conditions:** The dating period for each mAb, atoltivimab, maftivimab, and odesivimab, is (b) (4) months when stored at (b) (4) C. A stability protocol was included in the BLA to extend the drug substance shelf life.

C. Drug Product Inmazed 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.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management (see example in Attachment 3)

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance (General)	Measure of purity, impact on product safety and immunogenicity	DP manufacture [Redacted] (b) (4)	[Redacted]	(b) (4)
pH (as reconstituted DP) (General)	Impact on product stability and conformation	[Redacted] (b) (4)		
Particulate matter (visible and sub-visible) (General)	Impact on product safety and efficacy	DP manufacture [Redacted] (b) (4)		
Volume in Container (General)	Impact on efficacy	DP manufacture		
Protein Quantity (General)	Impact on efficacy	DP manufacture		
Identity (General)	Impact on efficacy	DP manufacture		

Endotoxin (Contaminant)	Safety (pyrogenic fever, increased immunogenicity risk) and purity	(b) (4)
Sterility (Contaminant)	Safety (infection), purity, and efficacy via degradation or modification of products by microbial contamination	
Container Closure Integrity (Contaminant)	Safety (maintenance of sterility during shelf life)	

- **Potency and Strength:** Inmazeb is supplied as atoltivimab, maftivimab, odesivimab-ebgn, injection, 241.67 mg of each mAb per 14.5 mL vial for a total 725 mg antibody per vial ((16.7 mg/16.7 mg/16.7 mg per mL) Potency is defined as the percent activity relative to the current combined atoltivimab, maftivimab, and odesivimab RS. The potency assays are the same as described for the DS.
- **Summary of Product Design:** Inmazeb is supplied as a sterile, single-dose, preservative-free liquid for injection, for intravenous use, in a 20 mL vial. It is formulated at 16.7 mg/mL altotivimab, 16.7 mg/mL, maftivimab, 16.7 mg/mL odesivimab in 10 mM histidine, 10% (w/v) sucrose, and 0.1% (w/v) polysorbate 80 at pH 6.0. The deliverable amount is 241.7 mg of each mAb per vial for a total of 725 mg.
- **List of Excipients:**
 - L-histidine: 4.8 mM, 10.8 mg/vial
 - L-histidine monohydrochloride monohydrate: 5.2 mM, 15.8 mg/vial
 - Sucrose: 10% w/v, 1450 g/vial
 - Polysorbate 80: 0.1% w/v, 14.5 mg/vial
- **Reference Materials:** (b) (4)
- **Manufacturing process summary:** (b) (4)

- **Container closure:** Inmazeb DP is stored in 20 mL (b) (4) glass vials, sealed with (b) (4) stopper, and an aluminum crimp seal cap with a flip-off button.
- **Dating period and storage conditions:** The dating period for Inmazeb is 30 months when stored at 2-8°C. A stability protocol was included in the BLA to extend the drug substance shelf life. Inmazeb will be included in the Strategic National Stockpile.

D. Novel Approaches/Precedents:

1. This is the first approval of a mAb cocktail, which is considered a fixed dose combination product.
2. A BLA was initially planned for submission in 2022; however, due to the early readout of the clinical study in the Democratic Republic of Congo showing efficacy of REGN-EB3, plans for submission of a BLA were expedited. Because of the urgent need for the product, Regeneron submitted the BLA describing the clinical manufacturing process rather than the proposed commercial process. The proposed commercial process will be submitted as a PAS subsequent to approval of the BLA.
3. (b) (4)
4. (b) (4)
5. (b) (4)
6. (b) (4)
7. Labeling:
 - a. The mAbs are listed in alphabetical order on the carton and container labels and in the Prescribing information
 - b. There is only one suffix attached to the final mAb in the list.
 - c. Strength is presented to specify the amount of each active ingredient "241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)" on the carton and container label.
 - d. In the Prescribing information, strength is presented to specify the amount of each active ingredient "241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)" in the following Sections Highlights Dosage Forms and Strengths; Section 3 Dosage Forms and Strengths; Section 11 Description; and Section 16 How Supplied/Storage and Handling.
8. At the recommended dose of 150 mg/kg/2hr, the potential endotoxin input for the proposed worst-case of (b) (4) mg/mL product concentration during infusion could be (b) (4) EU/kg/hr in a patient weighing 80 kg. This includes endotoxin input from both Inmazeb and the infusion solution ((b) (4) EU/mL USP endotoxin limit). To ensure that the USP endotoxin safety limit of (b) (4) will be maintained, Section 2.2 Preparation and Administration in the Prescribing Information includes a table showing infusion volumes and times by body weight and the worst-case product concentration during infusion was changed to 9.5 mg/mL.

9. In IR#12, dated July 27, 2020, the Agency requested that Regeneron submit an exception to include the expiration date on the REGN-EB3 vial label to avoid the necessity to submit a request and a relabeling protocol post-marketing, per 21 CFR 610.68 "A Strategic National Stockpile official or any entity that manufactures (including labeling, packing, relabeling, or repackaging), distributes, or stores a biological product that is or will be included in the Strategic National Stockpile may submit, with written concurrence from a Strategic National Stockpile official, a written request for an exception or alternative described in paragraph (a) of this section to the Center Director." The exception in 21 CFR610.68 does not include the carton. During the Late Cycle Meeting on August 31, 2020, Regeneron confirmed that they were working with BARDA and the SNS to submit this request. As of September 9, 2020, the request has not been submitted. A separate memo will be prepared should the request be submitted pre-licensure.

E. Any Special Product Quality Labeling Recommendations:

- a. Storage at 2-8°C, in original carton protected from light
- b. Do not freeze or shake
- c. For a combination product, ingredients are listed in alphabetical order
- d. Strength is presented to specify the amount of each active ingredient "241.7 mg/241.7 mg/241.7 mg per 14.5 mL (16.7 mg/16.7 mg/16.7 mg per mL)" on the carton and container label and in specified sections of the PI (See Precedents)
- e. The dose is 50 mg of atoltivimab, 50 mg of maftivimab, and 50 mg of odesivimab per kg of body weight; dose is calculated based on infusion volume per patient weight in kg (3 mL/kg) using the table in the prescribing information that provides the infusion volumes and infusion times per body weight to facilitate ease of dose calculation

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Drug substance manufacture	Regeneron Pharmaceuticals, Inc	945589711 1000514603	Approved – Based on PAI conducted on 11/4 – 11/8/2019	No FDA Form-483 issues	Approve
Bulk Drug Substance (BDS) storage	81 Columbia Turnpike Rensselaer, NY 12144				
Analytical testing (all methods except mycoplasma)					
Master Cell Bank (MCB) manufacture and					

primary storage					
Analytical testing (all methods except Pseudovirus neutralization, bioburden, endotoxin and (b) (4))	Regeneron Ireland Raheen Business Park Limerick, Ireland	985528196 3011684330	Approve – Based on Previous History		Approve – Based on Previous History
(b) (4)			Approve – Based on Previous History		Approve – Based on Previous History
			Approve – Based on Previous History		Approve – Based on Previous History
			Approve – Based on Previous History		Approve – Based on Previous History
			Approve – Based on Previous History		Approve – Based on Previous History
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)			Approve - based on previous history and waiver granted by OPMA and OBP		Approve – Based on Previous History
Final distribution release site and analytical	Regeneron Pharmaceuticals, Inc	945589711 1000514603	Approve – Based on Previous History		Approve – Based on Previous History

testing (all methods except sterility)	81 Columbia Turnpike Rensselaer, NY 12144				
Analytical testing (all methods except endotoxin, particulates, sterility, volume in container and CCI)	Regeneron Ireland Raheen Business Park Limerick, Ireland	985528196 3011684330	Approve – Based on Previous History		Approve – Based on Previous History
(b) (4)			Approve – Based on Previous History		Approve – Based on Previous History
			Approve – Based on Previous History		Approve – Based on Previous History

G. Facilities:

A pre-license inspection (PLI) of the proposed drug substance manufacturing site, Regeneron Pharmaceuticals, Inc. was conducted Nov 4-8, 2019. The inspection was classified as no action indicated (NAI). The proposed drug substance manufacturing facility is found to be acceptable to support the approval of BLA 761169.

The PLI of the drug product manufacturing site, (b) (4) was waived (b) (4) and the facility has an acceptable compliance history. The compliance recommendations for the other facilities described in the tables (section F), which are not inspected within scope of this BLA, are for approval.

H. Lifecycle Knowledge Management:

1. Drug Substance:
 - a. Protocols approved: Annual stability for DS, MCB and current Reference Standards
 - b. Outstanding review issues/residual risk: See PMCs
 - c. Future inspection points to consider:
 - Next inspection at Regeneron Rensselaer should review the (b) (4)
 - The upcoming PAS for Raheen should include an inspection

2. Drug Product

- a. Protocols approved: Annual stability for DP
- b. Outstanding review issues/residual risk: See PMCs
- c. Future inspection points to consider:
 - Verify that [REDACTED] ^{(b) (4)} the contract organization used by Regeneron Pharmaceuticals, Inc. for REGN-EB3 drug product manufacturing, implements the same in-process control criticality designation and ranges for process parameters and in-process product quality attributes as the approved process.

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

/s/

MARJORIE A SHAPIRO
09/09/2020 05:05:59 PM

QING ZHOU
09/09/2020 06:37:08 PM