CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761328Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: July 6,2023

1. Application/Product Information

BLA number	BLA 761328
Submission Type	Original Submission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	IND 118524
Review Designation	Standard Review (with early decision)
Applicant	AstraZeneca AB
Indication	Respiratory syncytial virus (RSV) infection
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Beyfortus Non-proprietary Name/Code Name: nirsevimab-alip OBP Naming: MAB HUMAN (IGG1) ANTI P03420 (FUS_HRSVA) [MEDI8897]
Drug Product Description	Nirsevimab is supplied as a sterile, preservative-free, liquid form in a single-dose pre-filled syringe (PFS) formulated as 100 mg/mL nirsevimab in (b) (4) mM L-histidine/L-histidine hydrochloride monohydrate, (b) (4) mM L-arginine hydrochloride, (b) (4) mM sucrose, 0.02% (w/v) polysorbate 80, pH 6.0. Nirsevimab is a human IgG1 κ monoclonal antibody with a YTE mutation in the Fc domain (to extend serum half-life), which binds specifically to the pre-fusion conformation of the respiratory syncytial virus (RSV) fusion (F) protein to prevent the infection of human cells by RSV.
Dosage Form	Solution for injection

Strength	50 mg/0.5 mL and 100 mg/1 mL		
Route of Administration	Intramuscular injection		
Primary Container Closure System	Pre-filled syringe		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Deborah Schmiel	Anshu Rastogi
	Drug product	Deborah Schmiel	Anshu Rastogi
	Immunogenicity Assay	Deborah Schmiel	Anshu Rastogi
	Facility	Wendy Tan	Zhong Li
	Microbiology	Wendy Tan	Maxwell Van Tassel
	RBPM	Andrew Shiber	
	ATL	Anshu Rastogi	
OPQ Issued Consults	None		

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

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761328 for Beyfortus manufactured by AstraZeneca AB. The data submitted in this application are adequate to support the conclusion that the manufacture of Beyfortus is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:

- **Drug Substance:** AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC; 633 Research Court, Frederick, MD, 21703); FEI: 3002617771
- **Drug Product:** (b) (4)

b. Fill size and dosage form:

Beyfortus is supplied as a 50 mg/0.5 ml and 100 mg/1 ml solution in a pre-filled syringe

c. Dating Period:

- **Drug Product:** 18 months at 2-8°C
- **Drug Substance:** (b) (4)
- **For packaged products:** Not packaged
- **Stability Option:**
  - For stability protocols:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: Beyfortus is exempted from lot release per FR 95-29960.

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

- Postmarketing commitment to provide data from real world shipping studies covering all transportation configurations, temperatures, modes, and routes of commercial transportation to evaluate product quality of the final drug product in the commercial container closure system pre- and post-shipment.

4. Basis for Recommendation

a. Summary:

Nirsevimab (Beyfortus) is indicated for the prevention of the RSV lower respiratory tract disease in neonates and infants entering or during their first RSV season and children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Nirsevimab is a human IgG1κ monoclonal antibody that binds specifically to the pre-fusion conformation of the RSV fusion (F) protein, neutralizing RSV to prevent the infection and infection-induced cell death of human cells by RSV. The Fc domain contains three amino acid substitutions (YTE mutation) enhancing its affinity to the neonatal Fc receptor

(FcRn) which extends serum half-life. The drug product is supplied as a sterile, preservative-free, liquid form in a single-dose PFS formulated as 100 mg/mL nirsevimab in (b) (4) mM L-histidine/L-histidine hydrochloride monohydrate, (b) (4) mM L-arginine hydrochloride, (b) (4) mM sucrose, 0.02% (w/v) polysorbate 80, pH 6.0; the PFS includes two presentations of 50 mg/0.5 mL and 100 mg/1 mL.

The potency of nirsevimab is evaluated though a bioassay that measures the ability of nirsevimab to prevent RSV infection-induced cell death in target human epithelial type 2 (HEp-2) cells by neutralizing the RSV. The Cell Titer-Glo™ luminescent cell viability assay system is used to determine the number of viable cells after RSV infection based on the quantitation of ATP present, an indicator of metabolically active cells. The amount of luminescence signal generated is proportional to the ATP present in the viable cells.

The drug substance (DS) manufacturing process consists of (b) (4) The drug product (DP) is manufactured at a (b) (4)

The overall manufacturing control strategy incorporates controls over raw materials, facilities and equipment, manufacturing processes, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product. The manufacturing processes and overall control strategies for Beyfortus (nirsevimab) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for manufacture at the AstraZeneca Pharmaceuticals Frederick Manufacturing Center (Frederick; MD; FEI: 3002617771) and (b) (4) proposed for DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from a product quality, facility, microbiology, and sterility assurance perspectives.

While data from real-world transport qualification studies for DS and simulated transport qualification studies for DP were provided in the submission to provide assurance that nirsevimab product quality is not impacted by shipping

conditions/hazards, a postmarketing commitment was issued to AstraZeneca to provide data from real-world shipping studies covering all transportation configurations, temperatures, modes, and routes of commercial transportation to evaluate product quality of the final drug product in the commercial container closure system pre- and post-shipment.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with PMCs/PMRs**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Adequate**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:

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

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved

1. Future Working Cell Bank Qualification
2. Nirsevimab Process Intermediate Holds (Commercial scale Microbial Validation)
3. (b) (4)
4. (b) (4)
5. Primary and Working Reference Standard Stability Protocol
6. Drug Substance Stability Tests and Testing Intervals (Shelf-life Extension Protocol)

7. Drug Substance Post-Approval Stability Testing Commitment
8. Comparability Protocol - Drug Substance Manufacturing Scale Increase

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

c. Drug Product:

i. Protocols approved:
1. Drug Product Stability Tests and Testing Intervals (Shelf-life Extension Protocol)
2. Drug Product Post-Approval Stability Testing Commitment

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

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

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

/s/

ANSHU RASTOGI
07/06/2023 11:27:30 AM

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	July 6, 2023
Assessor:	Scott Dallas, RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Deborah Schmiel, PhD Product Quality Assessor OBP/Division of Biotechnology Review and Research 1
Application:	BLA 761328
Applicant:	AstraZeneca AB
Submission Date:	September 26, 2022
Product:	BEYFORTUS (nirsevimab-alip)
Dosage form(s):	injection
Strength and Container-Closure:	50 mg/0.5 mL in a single-dose prefilled syringe, and 100 mg/1 mL in a single-dose prefilled syringe
Purpose of assessment:	The Applicant submitted a biologics license application for the prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in: • Neonates and infants born during or entering their first RSV season. • Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.
Recommendations:	The prescribing information, patient information, container labels, and carton labeling 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

DISCUSSION

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

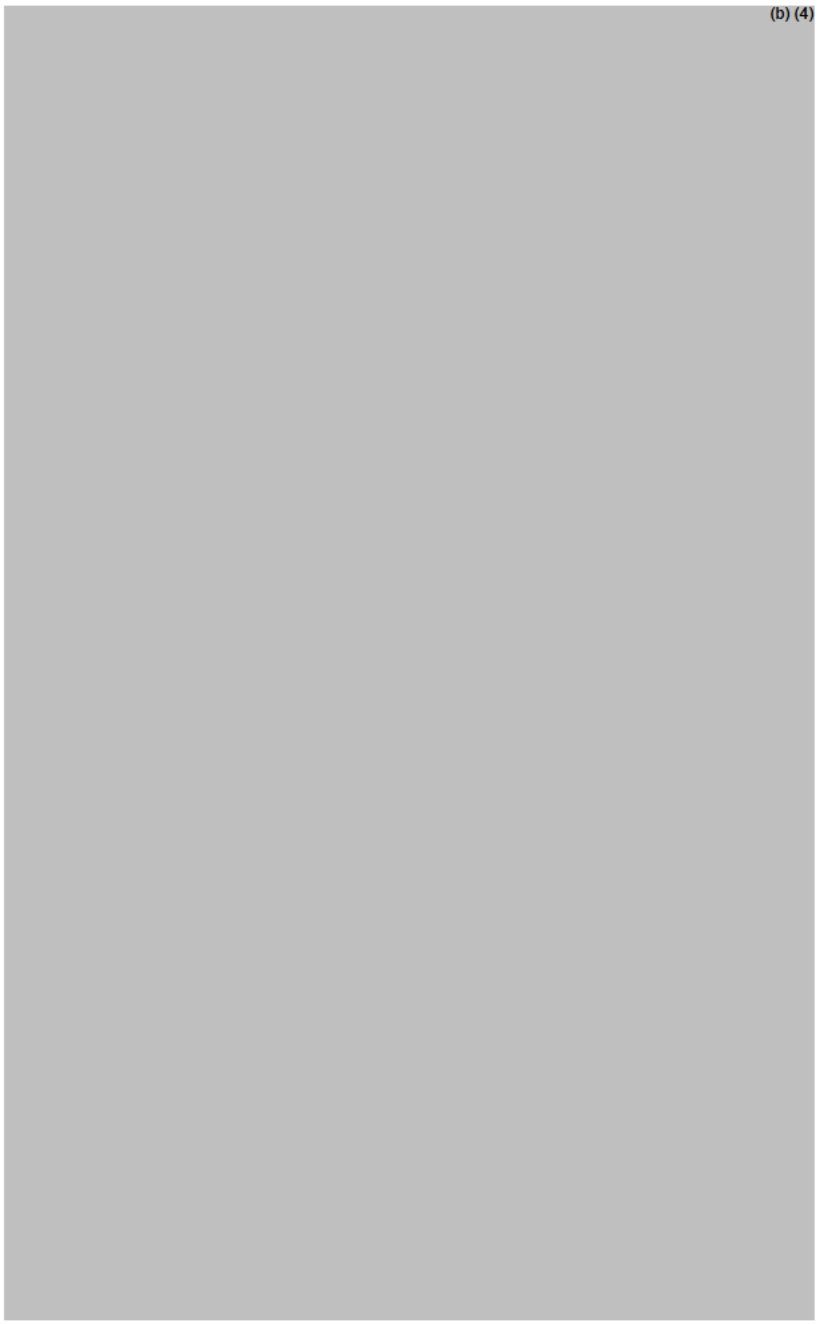
CONCLUSION

The prescribing information and patient information submitted on June 30, 2023, and the container labels, and carton labeling submitted on June 20, 2023 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Patient Information (submitted on September 26, 2022) \\CDSESUB1\EVSPROD\bla761328\0001\m1\us\annotated-draft-label-nirsevimab.pdf
- (b) (4)



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

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

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(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:

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

Comment/Recommendation: The label is small and could be considered a partial label. Thus, the qualifying phrase "Manufactured by" and the U.S. license number are not required.

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

[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."

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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:
To applicant: Revise the '100 mg/1 mL' concentration statement to '100 mg/mL' in accordance with USP General Chapter <7>. Applicant's Response: The applicant acknowledged the FDA request to update the concentration statement to '100 mg/mL' and updated the artworks for carton and container labeling accordingly. OBP Labeling: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: The product does not need a Medication Guide.

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

Comment/Recommendation:

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

Comment/Recommendation:

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: The product is supplied in a prefilled syringe.

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes

	☐ No ☐ N/A

Comment/Recommendation:

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

Comment/Recommendation: The label is small and could be considered a partial label. Thus, the route of administration is not required.

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

Comment/Recommendation: The label is small and could be considered a partial label. Thus, the NDC is not required on the container label. The NDC appears as part of the readable information for the bar code.

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

Comment/Recommendation:

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

Comment/Recommendation: The label is small and could be considered a partial label. Thus, the package type term is not required.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Add a linear barcode to the prefilled syringe container label and ensure the linear bar code is surrounded by enough blank space to facilitate proper scanning, per 21 CFR 201.25 and 21 CFR 610.67.

AstraZeneca acknowledges the FDA recommendation to include a linear barcode to the prefilled syringe container label. However, due to the limitations of the label size and challenges with availability of white space, AstraZeneca proposes that the use of a Partial label in line with 21CFR610.60(c) may be more appropriate.
21CFR610.60(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.

To applicant: We acknowledge your comment that a bar code cannot be added due to the small size of the container label. Per 21 CFR 201.25(d), an exemption request for a bar code requirement can be submitted. The exemption request must document why:(i) compliance with the bar code requirement would adversely affect the safety, effectiveness, purity or potency of the drug or not be technologically feasible, and the concerns underlying the request could not reasonably be addressed by measures such as package redesign or use of overwraps; or (ii) an alternative regulatory program or method of product use renders the bar code unnecessary for patient safety.

Additionally, the request should include supporting documentation and statements to support the request such as:

- Images of the drug container and dimensions
- Images of the carton label that contains the drug
- How the drug is supplied and packaged
- Whether the drug used only at the time of use
- Whether there are distinctive characteristics of the drug that would aid in verification of the drug before administration
- Whether other barcodes exist on the immediate container and other levels of packaging (e.g., 2D DataMatrix barcode to satisfy DSCSA product identifier requirements)

The request can be sent CDER Barcode Questions CDERBarcodeQuestions@fda.hhs.gov

Applicant's Response: The applicant included a limited GS1 barcode encoding the National Drug Code as per the requirements under 21 CFR 201.25(c).

OBP Labeling: The applicant's revision is acceptable.

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:

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

Comment/Recommendation:

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: The label is small and could be considered a partial label. Thus, a dosage statement is not required.

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

Comment/Recommendation: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

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: The label is small and could be considered a partial label. Thus, a storage statement is not required.

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

Comment/Recommendation:

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:

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
Recommended labeling practices (U.S license number for container bearing a partial label[7])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

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

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

[7] 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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation: This product is only available as a single-dose syringe.

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

Comment/Recommendation: Displays a "no preservative" statement.

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

Comment/Recommendation:

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:
To applicant: Revise the '100 mg/1 mL' concentration statement to '100 mg/mL' in accordance with USP General Chapter <7>.

Applicant's Response: The applicant acknowledged the FDA request to update the concentration statement to '100 mg/mL' and updated the artworks accordingly.

OBP Labeling: The applicant's revisions are acceptable.

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:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:
The product is not made with natural rubber latex.

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:
To applicant: Please revise the Contents statement to read: Contents: Each 0.5 mL contains 50 mg nirsevimab-alip, arginine hydrochloride (8 mg), histidine (1.1 mg), L-histidine hydrochloride monohydrate (1.6 mg), polysorbate 80 (0.1 mg), sucrose (21 mg), and water for injection (USP). The pH is 6.0. Contents: Each 1 mL contains 100 mg nirsevimab-alip, arginine hydrochloride (17 mg), histidine (2.2 mg), L-histidine hydrochloride monohydrate (3.3 mg), polysorbate 80 (0.2 mg), sucrose (41 mg), and water for injection (USP). The pH is 6.0. Applicant's Response: The applicant revised the contents statements as requested. OBP Labeling: The applicant's revisions are acceptable.

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

Comment/Recommendation: The drug substance is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology, and no information is required to be on the carton labeling.

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

Comment/Recommendation:

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

To applicant: Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable.

Applicant's Response: The applicant removed the statement "No U.S. standard of potency" .

OBP Labeling: The applicant's revision is acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:
The bar code is on a side panel.

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:

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

Comment/Recommendation:
To applicant: Include a National Drug Code to the carton labeling.

Applicant's Response: The applicant acknowledges the FDA recommendation to include the National Drug Code on the carton labeling. The applicant indicated that the National Drug Code will be raised by the Distributor and once the National Drug Code is available to AstraZeneca, the carton artworks will be updated to show the National Drug Code instead of the current place holder 'NDC XXXX-XXXX-XX'.

On June 20, 2023 the applicant submitted carton labeling displaying an NDC.

OBP Labeling: The applicant's revisions are acceptable.

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

Comment/Recommendation: No preparation instructions are needed for the prefilled syringe.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:
To applicant: Revise the net quantity statements on the Principal Display Panel (PDP) from "(1 or 5) Single-dose prefilled syringe" to read "(One or Five) 0.5 mL single-dose prefilled syringe" or "(One or Five) 1 mL single-dose prefilled syringe" to clarify the net quantity statement.

Applicant's Response: The applicant revised the net quantity statements as requested.

OBP Labeling: The applicant's revisions are acceptable.

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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

Comment/Recommendation:

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:

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

Comment/Recommendation:

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:
To applicant: [redacted] (b) (4) was deleted from this section, because this information is not required for this section. In addition, revise the appearance of the product strength 100 mg/1 mL to read 100 mg/mL throughout the labeling. Refer to FDA Guidance titled "Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors" dated May 2022 for more information.

[redacted] (b) (4)

Applicant's Response: The applicant revised the statement as requested.

OBP Labeling: The applicant's revision is acceptable.

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:
To applicant: Revised to include the required statement per 21 CFR 201.57(c)(3)(iv).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."

Applicant's Response: The applicant included the statement as requested.

OBP Labeling: The applicant's revision is acceptable.

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:
To applicant: (b) (4) was deleted from this section, because this information is not required for this section.

(b) (4)

Applicant's Response: The applicant revised the statements as requested.

OBP Labeling: The applicant's revisions are acceptable.

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:

To applicant: FDCA 502(e) requires use of the established name for ingredients and drug products. FDCA recognizes USP as the official compendium. Thus, the names of the inactive ingredients were revised to appear as their compendial names.

(b) (4)

Applicant's Response: The applicant revised the statements as requested.

OBP Labeling: The applicant's revisions are acceptable.

To applicant: Revised the first sentence to include the established pharmacological class.

(b) (4)

Applicant's Response: The applicant revised the sentence as requested.

OBP Labeling: The applicant's revision is acceptable.

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

Comment/Recommendation:

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:
To applicant: Revised to easier see the quantity of the product at the beginning of each bullet with the NDC appearing at the end of each bulleted statement.

(b) (4)

To applicant: Revised to prevent the package type term "single-dose" from being confused with the usage of the product.

(b) (4)

Applicant's Response: The applicant revised the statements as requested.

OBP Labeling: The applicant's revisions are acceptable.

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

Comment/Recommendation:

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

PATIENT INFORMATION LABELING	
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:
To applicant: Revised the names of the inactives ingredients to appear as their compendial names.

Applicant's Response: The applicant revised the names of the ingredients as requested.

OBP Labeling: The applicant's revisions are acceptable.

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

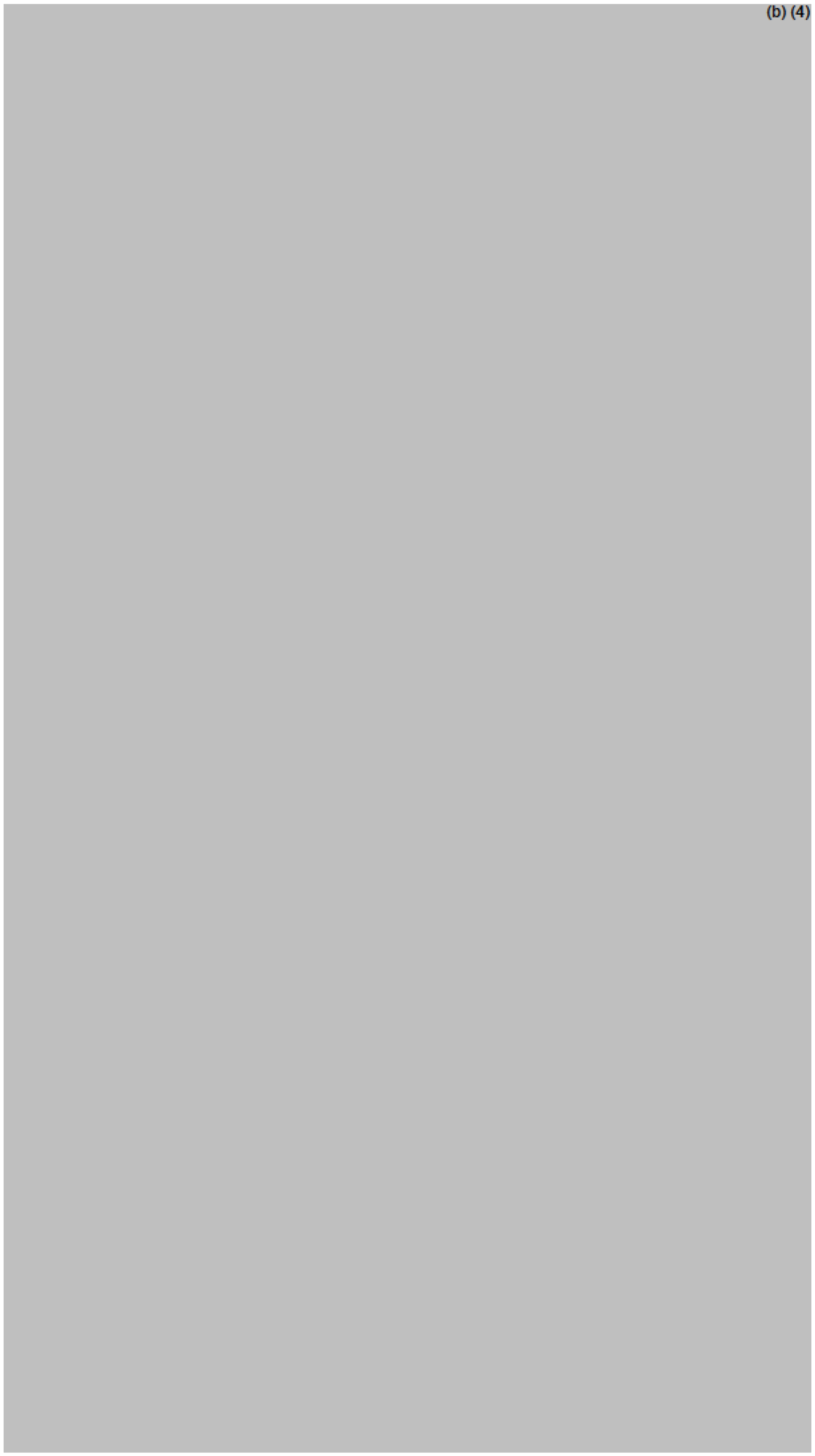
Comment/Recommendation:
To applicant: Relocated the U.S. License number to appear directly below the manufacturer information, because the license is granted to the manufacturer and not the distributor.

Applicant's Response: The applicant relocated the U.S. License number as requested.

OBP Labeling: The applicant's revisions are acceptable.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information and Patient Information (submitted on June 30, 2023) \\CDSESUB1\EVSPROD\bla761328\0089\m1\us\nonannotated-draft-label-nirsevimab.docx



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

Scott Dallas

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Date: 7/06/2023 02:57:59PM
GUID: 508da712000294048aa136a18a6af06a

Deborah Schmiel

Digitally signed by Deborah Schmiel
Date: 7/06/2023 11:35:14PM
GUID: 525e939c0003b510f311aa53c1abf18e