CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761498Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: August 29, 2025

1. Application/Product Information

BLA number	761498
Submission Type	Original submission
Regulatory Pathway	Interchangeable Biosimilar Application 351(k)
Associated IND	153821
Review Designation	Standard review (Expedited review requested)
Applicant	Celltrion, Inc.
Indication	Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis, Systemic Juvenile Idiopathic Arthritis, and Coronavirus Disease 2019
Rx/OTC dispensed	Rx
Drug Product Name	AVTOZMA
	tocilizumab-anoh/CT-P47
	MAB HUMANIZED (IGG1) ANTI P08887 (IL6RA_HUMAN) [CT-P47]
Drug Product Description	AVTOZMA (tocilizumab-anoh) injection is a sterile, clear to slightly opalescent, colorless to yellow, preservative-free solution with a pH of 6.0 for subcutaneous use. Each single-dose 0.9 mL prefilled syringe (PFS) with a needle safety device or single-dose 0.9 mL autoinjector (AI) contains 162 mg tocilizumab-anoh in histidine (0.7 mg), L-histidine hydrochloride monohydrate (1.0 mg), methionine (8.1 mg), polysorbate 80 (0.2 mg), threonine (17.2 mg), and Water for Injection, USP. Tocilizumab-anoh is a recombinant, humanized IgG1k monoclonal antibody directed against human interleukin 6 receptors (IL-6R) and binds to the IL-6 binding site of both soluble and membrane-bound IL-6R (sIL-6R and mIL-6R).
Dosage Form	Injection, solution
Strength	162 mg/0.9 mL (180 mg/mL)

Route of Administration	Subcutaneous (SC)		
Primary Container Closure System	PFS		
Device Information	PFS with a needle safety device AI		
Co-packaged Product Information	Not applicable		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Product quality	Deepa Raghu	Bazarragchaa Damdinsuren
	Microbiology and facility	Della Shin	Zhong Li
	RBPM	Anita Brown	
	ATL	Bazarragchaa Damdinsuren	
OPQ Issued Consults	A consult to CDRH for device components was performed under original BLA 761420.		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761498 for Avtozma manufactured by Celltrion, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Avtozma is well-controlled and leads to a product that is pure and potent. The comparative analytical data support a demonstration that Avtozma is highly similar to US-licensed Actemra, notwithstanding minor differences in clinically inactive components. 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:**
  (b) (4)
- **Drug Product:**
  Celltrion Pharm, Inc. (FEI: 3012279978)

82, 2 Sandan-ro, Ochang-eup, Cheongwon-go, Cheongju, Republic of Korea

b. Fill size and dosage form:
Injection, solution in single-dose PFS with a needle safety device and in single-dose prefilled AI: 162 mg/0.9 mL

c. Dating Period:
- Drug Product:
  36 months when stored at 5 ± 3°C
- Drug Substance:
  (b) (4) months when stored at (b) (4) °C
- For packaged products: Not packaged
- Stability Option:
  - For stability protocols:
    - 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.

d. Exempt from lot release:
- Yes
- Rationale, if exempted: Avtozma 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
None

4. Basis for Recommendation
a. Summary: Avtozma (tocilizumab-anoh, CT-P47) is a proposed biosimilar to US-licensed Actemra (US-Actemra) that is intended to be delivered by the same routes of administration (SC) for the same indications as the US-Actemra reference product. The comparative analytical assessment (CAA) data submitted under BLA 761420 support the demonstration that Avtozma is highly similar to US-Actemra, notwithstanding minor differences in clinically inactive components and that the analytical portion of the scientific bridge to justify the use of clinical data derived from EU-approved RoActemra was established.

Tocilizumab is a recombinant, humanized IgG1 monoclonal antibody that specifically binds to the IL-6 binding site of both sIL-6R and mIL-6R and

blocks the activity of IL-6. This leads to down-regulation of IL-6-driven cellular functions. The biological activity of CT-P47 is evaluated on its capability to inhibit the IL-6-mediated cell proliferation of DS-1 human B-lymphoma cell line.

All proposed manufacturing and testing facilities are acceptable based on their current GMP compliance status and recent relevant inspectional activity. Note that the pre-license inspectional activities of the manufacturing facilities were performed under the original BLA 761420.

The assessment of manufacturing information provided in this application (that is the same under the approved BLA 761420) has concluded that the methodologies and processes used for DS and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product. The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product and the OPMA assessors are recommending approval for this BLA from a sterility assurance and microbiology product quality perspective.

The DS manufacturing process and controls information is cross-referenced to BLA 761420. The DS is stored (b) (4).
The Avtozma DP-SC manufacturing includes (b) (4) The naked PFSs then assembled with finger flange and safety guard or AI, and labeled and packaged. The final DP-SC is stored at 5 ± 3°C for long term storage.

The assessment of immunogenicity assays to detect binding and neutralizing anti-drug antibodies (ADAs) to tocilizumab in the clinical studies to support this BLA was performed under BLA 761420. The assessment concluded that the assays were adequately validated and suitable for their intended purpose. Individual assessment memos for each discipline are located in separate documents in Panorama.

b. Subdiscipline Recommendation:

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

*The CMC information for these subdisciplines is provided under BLA 761420 and cross-referenced. The product quality and immunogenicity assay assessments performed for BLA 761420 are applicable to support the current BLA.

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 Avtozma (i.e., there is no specific test method described in regulation for Avtozma that establishes an official standard of potency). We next considered whether potency is a factor for Avtozma 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 Avtozma for purposes of § 610.61(r) because lot variability is not a concern for Avtozma as Avtozma'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:
   * Refer to BLA 761420

   c. Drug Product (SC):
      i. Protocols approved for:
         1. Annual stability protocol and stability protocol for the extension of DP shelf-life (3.2.P.8.2 and 3.2.P.8.1)
         2. DP shipping validation protocol for change in shipping conditions (3.2.R.6)
      ii. Residual risk: No
      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.

Appendix. Comparative Analytical Assessment Summary

A. Analytical Assessment Overview and Conclusions

The Comparative Analytical Assessments (CAAs) between CT-P47, U.S.-licensed Actemra, and E.U.-approved RoActemra were performed under BLA 761420. The CAA concludes that the comparative analytical data support a demonstration that Avtozma is highly similar to US-licensed Actemra, notwithstanding minor differences in clinically inactive components.

B. Same Strength

CT-P47 under the current BLA has the same dosage forms and routes of administration as US-licensed Actemra. US-Actemra is available at these strengths: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL (all 20 mg/mL) in vials for further dilution prior to intravenous infusion, and 162 mg/0.9 mL in a prefilled syringe or prefilled autoinjector. In this BLA the Applicant is seeking approval of 180 mg/mL CT-P47 in 162 mg/0.9 mL prefilled syringe or autoinjector. Comparative concentration (mg/mL) was assessed as part of the CAA. The extractable volume and fill weight data were also assessed in the context of manufacturing controls. Based on the comparative concentration data and manufacturing data, the 180 mg/mL CT-P47 in 162 mg/0.9 mL prefilled syringe or autoinjector have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as the corresponding strength of US-Actemra. Each strength of CT-P47 prefilled syringe/autoinjector is the same as that of US-Actemra.

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/

BAZARRAGCHAA DAMDINSUREN
08/29/2025 12:09:19 PM

PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
Memorandum of Review to the File

Application ID	BLA 761498
Submission Type	Original BLA
Drug Product Name	AVTOZMA (CT-P47)
Strengths	162 mg/0.9 mL (SC)
Dosage Form	Solution for injection
Administration Route	Subcutaneous
Indication	Rheumatoid Arthritis
Applicant Name	CELLTRION, Inc.
US License Number	1996
Application Type	351 (k)
Primary Reviewer	Della Shin, Ph.D., Pharmaceutical Scientist, OPMA/DPMAVI
Secondary Reviewer	Maxwell Van Tassell, PhD, SPQA, OPMA/ DPMAV (microbiology) Zhong Li, Ph.D., SPQA, OPMA/DPMAVI (facility)
Goal Date	5/18/2026

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology and sterility assurance perspective and is recommended for Approval.
- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OPQAIII.

Application Submission Background

Reviewer's Comment: For Information

CT-P47 is proposed for manufacture in the following dosage forms under BLA-761498:
• 162 mg in 0.9 mL (180 mg/mL) solution for SC injection in PFS with safety guard (PFS-S)
• 162 mg in 0.9 mL (180 mg/mL) solution for SC injection in auto-injector (AI)

The subcutaneous administration of CT-P47 was previously approved alongside the intravenous formulation under BLA 761420 on January 24, 2025. Due to changes in business and marketing strategy, CELLTRION has elected to separate the BLA approvals for intravenous and subcutaneous administration.
Accordingly, this new BLA application has been submitted for subcutaneous administration only. The documents included in this application are identical to those previously reviewed and approved under the previous BLA 761420 submission. Therefore, please refer to the review memo for BLA 761420 for evaluation of Module 3.

FACILITY ASSESSMENT

Facility name and address	FEI	Responsibilities and profile code(s)	Status
CELLTRION, Inc. 23, Academy-ro, Yeonsu-gu , Incheon, N/A, Republic of Korea, 22014	3005241015	Release testing of CT-P47 drug substance; Stability testing of CT-P47 drug substance; Testing of the MCB and WCB; Storage of the MCB and WCB; Testing of CT-P47 unprocessed bulk; Release testing of CT-P47 drug product; Stability testing of CT-P47 drug product; || 356h Status: Active LBI, LCP, LMN, LMS	Approve - Based on Previous History
CELLTRION Inc. 20, Academy-ro, 51 beon-gil, Yeonsu gu , Incheon, N/A, Republic of Korea, 22014	3005241015	Release testing of CT-P47 drug substance; Stability testing of CT-P47 drug substance; Release of CT-P47 drug substance; Testing of the MCB and WCB; Storage of the MCB and WCB; Testing of CT-P47 unprocessed bulk; Release testing of CT-P47 drug product (SC); Stability testing of CT-P47 drug product (SC); Release of CT-P47 drug product (SC) || 356h Status: Active LBI, LCP, LMN	Approve - Based on Previous History
(b) (4)			No Evaluation Necessary
			No Evaluation Necessary
			No Evaluation Necessary
			Approve - Based on Previous History
CELLTRION Pharm, Inc. 82 2 Sandan-ro, Ochang-eup, Cheongwon-gu , Cheongju, Chungcheongbuk-do, Republic of Korea, 28117	3012279978	Production of CT-P47 drug product (SC) (uDP); Assembly and secondary packaging (labelling and cartonning) of CT-P47 drug product (SC) (PFS-S and AI); Release testing of CT-P47 drug product (SC); Stability testing of CT-P47 drug product (SC) || 356h Status: Active IDD, SVS	Approve - Based on Previous History
(b) (4)			Approve - Based on Previous History

BLA STN 761498

Avtozma [tocilizumab-anoh]

Manufacturer: Celltrion, Inc.

Deepa Raghu, Ph.D., Primary Assessor
Bazarragchaa Damdinsuren, M.D., Ph.D., Application Technical Lead

Division of Product Quality Assessment XVI
Office of Product Quality Assessment III (OPQA III)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OPQA III CMC Assessment Data Sheet

1. BLA#: 761498

2. Assessment Date: 8/29/2025

3. Primary Assessment Team:

Product Quality Team:

OPQ/OPQAIII:	Deepa Raghu, Bazarragchaa Damdinsuren (ATL)
OPQ/OPMA:	Della Shin (DS and DP), Zhong Li (Facility TL)
OPQ/OPRO:	Anita Brown (RBPM)
Clinical:	Raquel Tapia, Thomas Herndon (TL)
Pharmacology/Toxicology:	Vinay Patil, Carol Galvis (TL)
Clinical Pharmacology:	Lei He, Ping Ji (TL)
Statistics:	NamHee Choi, Elena Rantou (TL)
OTBB PM:	Anh-Thy Ly

4. Major GRMP Deadlines:

   a. Submission received: 5/19/2025
   b. Filing date: 7/18/2025
   c. BsUFA date: 5/19/2026

5. Drug Product Name/Code/Type:

   a. Proprietary/Trade Name: AVTOZMA
   b. Non-Proprietary Name/USAN: tocilizumab-anoh
   c. CAS Name: 375823-41-9
   d. Common Name: CT-P47
   e. INN Name: Tocilizumab-anoh
   f. OPQAIII systematic name: MAB HUMAN (IGG1) ANTI 08887 (IL6A_HUMAN) [CT-P47]

6. Pharmacological Category: Recombinant humanized IgG1 monoclonal antibody directed against human soluble and membrane-bound IL-6 receptor. CT-P47 is a biosimilar to US-licensed Actemra (humanized monoclonal IgG1 antibody).

7. Dosage Form: Injection, solution in single-dose prefilled syringe with safety guard (PFS) and single-dose prefilled autoinjector (AI)

8. Strength/Potency:
   (i): The concentration/strength of the Drug Product: 162 mg/0.9 mL (180 mg/mL)
   (ii): Type of potency assay(s): Inhibition of IL-6-induced cell proliferation

9. Route of Administration: Subcutaneous injection

10. Inspectional Activities: The inspectional activities for manufacturing facilities are completed under BLA 761420 which are applicable to this BLA.

11. Consults Requested by OPQAIII: No consult at this time. The prior assessments of device components of AI and PFS by CDRH under BLA 761420 are applicable to this BLA.

12. Quality by Design Elements: None

13. Precedents: None

14. Administrative:

Name and Title	Signature and Date
Bazarragchaa Damdinsuren, M.D., Ph.D. Application Technical Lead	See attached
Deepa Raghu, Ph.D., Primary assessor	See attached

Primary Assessor Summary Recommendation:

The Office of Product Quality Assessment III (OPQA III) recommends approval of the BLA 761498 for Avtozma (tocilizumab-anoh, CT-P47) manufactured by Celltrion, Inc. The data submitted in this BLA, specifically Module 3 DP-SC sections, is identical to the information assessed in BLA 761420 (and approved on 1/24/2025) for the manufacture of Avtozma (tocilizumab-anoh) for subcutaneous (SC) administration with cross-reference to some of the sections in Modules 3, 4 and 5 of BLA 761420. Note that the CMC information is specifically referring to submissions submitted between 1/26/2024 and 12/19/2024.

Assessor's comments: *The applicant has submitted this original BLA for Avtozma SC presentations cross-referencing to some of the sections in Modules 3,4 and 5 of BLA 761420 (see cover letter) and with a request for voluntary revocation of license for SC administration from BLA 761420 (SN:0043). The applicant has included the CMC information of CT-P47 DP SC formulation into Module 3 of this BLA. I have verified that all the information provided in this BLA is the same as the contents in the approved original BLA 761420 as of 12/19/2024.*

The applicant further stated that there are planned supplements under BLA 761420 that is relevant to this BLA (CMC-related supplements that will impact the SC administration are summarized below):

Category	Details	Status	Impact on BLA 761498
CBE-30	(b) (4)	Not yet submitted	Sections in 3.2.S will be updated, which are cross referenced in this application
PAS (Supplement-3)	* Addition of a new DS manufacturing site (Celltrion Plant (b) (4) Republic of Korea) for CT-P47. * Addition of CCS for CT-P47 DS. * Change of CT-P46 DS and DP specification for IEC-HPLC assay. * Addition of Celltrion Plant (b) (4) for (b) (4) testing.	*Submitted on 6/27/2025*	Sections 2.3.S and 3.2.S will be updated, which are cross-referenced in this application

As of the date of this assessment, the applicant has submitted Supplement-3 to BLA 761420. Based on the discussions between OPQAIII, OTBB, and OPRO, the submission will not preclude action on the current BLA 761498. OTBB plans to request the applicant to submit a new supplement for BLA 761498 that cross references BLA 761420 Supplement-3; this will further align the BLAs in regards to the DS manufacturing and controls.

Deepa Raghu

Digitally signed by Deepa Raghu
Date: 8/29/2025 11:34:53AM
GUID: 629f525a0001e480749408148110l6a6

Bazarragchaa Damdinsuren

Digitally signed by Bazarragchaa Damdinsuren
Date: 8/29/2025 11:46:37AM
GUID: 50afa2ce0005f62310093b8bdc00b898

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	July 15, 2025
Assessor:	Jennifer Kim, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Deepa Raghu, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761498
Applicant:	CELLTRION, Inc.
Submission Date:	May 19, 2025
Product:	Avtozma (tocilizumab-anoh)
Dosage form(s):	Injection
Strength and Container-Closure:	162 mg/0.9 mL in a single-dose prefilled syringe 162 mg/0.9 mL in a single-dose prefilled autoinjector
Purpose of assessment:	The Applicant submitted a biologics license application to separate the BLA approval for intravenous and subcutaneous administration of Avtozma (tocilizumab-anoh) and unbranded Tocilizumab-anoh which were approved under BLA 761420 as an interchangeable biosimilar to US-licensed Actemra (BLA 125276 and BLA 125472). This new BLA 761498 is submitted for subcutaneous administration only.
Recommendations:	The prescribing information, medication guide, instructions for use, container labels, and carton labeling are **acceptable** from an OPQA III labeling perspective.

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

n/a = not applicable for this assessment

DISCUSSION

We previously assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations.[1] Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

Container[2] Label Evaluation and Package[3] Labeling Evaluation

The content and format of proposed container label and carton labeling are the same as labeling found acceptable for BLA 761420.

Prescribing Information Evaluation

The content and format of product quality-related sections of PI are the same as labeling found acceptable for BLA 761420.

Medication Guide Evaluation

The content and format of product quality-related sections of MG are the same as labeling found acceptable for BLA 761420.

Instructions for Use Evaluation

The content and format of product quality-related sections of IFU are the same as labeling found acceptable for BLA 761420.

CONCLUSION

The prescribing information, medication guide, instructions for use, container labels, and carton labeling submitted on May 19, 2025, were assessed and found to be acceptable (see Appendix A) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed and Acceptable Labeling

- Prescribing Information (submitted on May 19, 2025)
  \\CDSESUB1\EVSPROD\bla761498\0001\m1\us\draft-labeling-text-avtozma-clean.docx

  \\CDSESUB1\EVSPROD\bla761498\0001\m1\us\draft-labeling-text-unbranded-clean.docx

[1] Kim, J. Labels and Labeling Review. BLA 761420 labels and labeling assessment. Silver Spring (MD): FDA, CDER, OPQ, OPQA III (US); 2025 January 23. 68(Number of pages).

[2] 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.

[3] 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.

- Medication Guide and Instructions for Use (submitted on May 19, 2025)
  \\CDSESUB1\EVSPROD\bla761498\0001\m1\us\draft-labeling-text-mg-ifu-avtozma-clean.docx

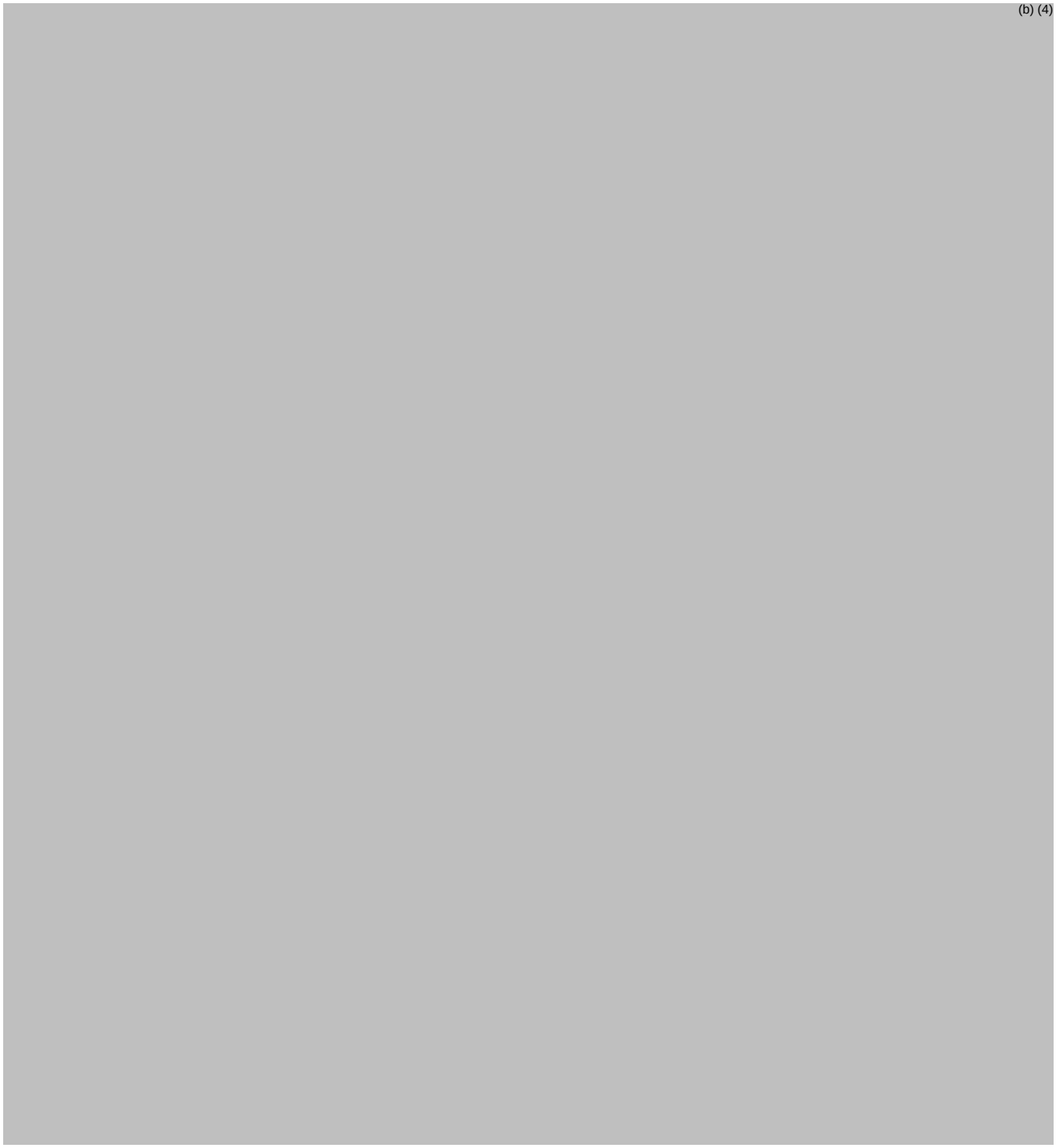
  \\CDSESUB1\EVSPROD\bla761498\0001\m1\us\draft-labeling-text-mg-ifu-unbranded-clean.docx

- Container Labels (submitted on May 19, 2025)

(b) (4)

- Carton Labeling (submitted on May 19, 2025)

(b) (4)



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

Jennifer Kim

Digitally signed by Jennifer Kim
Date: 7/15/2025 03:04:22PM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Deepa Raghu

Digitally signed by Deepa Raghu
Date: 7/15/2025 04:27:53PM
GUID: 629f525a0001e480749408148110l6a6