

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761312Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 7/14/2024
Version 2 – 7/30/2024 – with PMCs

1. Application/Product Information

BLA number	761312
Submission Type	BLA Class 2 Resubmission
Regulatory Pathway	NME 351 (a)
Associated IND(s)/BLA	IND 110489; IND 004682; BLA 103767
Review Designation	Standard
Applicant	Citius Pharmaceuticals, Inc.
Indication	For the treatment of adult patients with persistent or recurrent cutaneous T-cell lymphomas after at least 1 prior systemic therapy, (b) (4)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: Lymphir
	Non-proprietary Name: (Denileukin diftitox-cxdl)
	Development code Name: E7777
	OBP Naming: FUS: RPROT P00587 (DTX_COROM) or P00588 (DTX_CORBE); RPROT P60568 (IL-2_HUMAN) [E7777]
Drug Product Description	LYMPHIR is supplied as a sterile, preservative-free, white, lyophilized cake in a single-dose vial. The nominal content of each vial is 300 mg of denileukin diftitox, (b) (4) mg trehalose dihydrate, 3.0 mg methionine, 1.2 mg polysorbate 20, 0.04 mg edetate disodium, 4.2 mg citric acid monohydrate. Sodium hydroxide is used to adjust the pH of the formulation buffer. The lyophilized DP is to be reconstituted with 2.1 mL of water for injection (WFI) to make a (b) (4) solution at 150 µg/mL denileukin diftitox concentration for further dilution prior to IV administration.

	Denileukin diftitox is a recombinant IL-2 directed cytotoxin cytotoxin made up of diphtheria toxin fragments A and B (Met₁-Thr₃₈₇) fused to human interleukin 2 (Ala₁-Thr₁₃₃) and produced (b) (4) in <i>E. coli</i>. The diphtheria toxin fragments A and B are at the N-terminal of the protein (b) (4)		
Dosage Form	Lyophilized cake, for solution, for injection.		
Strength	300 mcg/vial		
Route of Administration	Intravenous infusion		
Primary container closure system	Vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Subdiscipline	Primary	Secondary
	Drug substance	Jee Chung	Chana Fuchs
	Drug product	Jee Chung	Chana Fuchs
	Immunogenicity Assay	Jee Chung	Chana Fuchs
	Facility	DS - Charles Kuo DP -Chani Broner	Zhong Li
	Microbiology	DS - Charles Kuo DP -Chani Broner	Maxwell Van Tassell

	RBPM	Kristine Leahy
	ATL	Chana Fuchs

2. Recommendation and Conclusion on Approvability

Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality (OPQ), CDER recommends approval of BLA 761312 for Lymphir (Denileukin diftiox-cxdl) manufactured by Citius Pharmaceuticals, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Lymphir is well-controlled and will lead 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:** (b) (4)
(FEI (b) (4))

• **Drug Product:**

- (b) (4) (FEI: (b) (4)).
- Labeling and secondary packaging will take place at (b) (4).
(FEI: (b) (4)).

b. Fill size and dosage form: Lymphir is supplied as a 300 mcg lyophilized cake in a single-dose vial.

c. Dating Period:

• **Drug Product:** 60 months when stored at 2-8°C, protected from light.

(b) (4)

- **For packaged products:** N/A
- **Stability Option:**

- Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
- We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

- Yes
- Rationale: Lymphir is exempted from lot release per FR 95-29960.

1. Update the process control strategy for E7777 drug substance (DS) to include (b) (4) and provide method validation data for each sample from three independent DS batches.
2. Provide qualification data from three DS batches for the bioburden test using 10 mL sample volumes (b) (4) and update the BLA with the revised bioburden alert and action limits to reflect the 10 mL sample.

a. Summary:

Denileukin diftitox has the same sequence and the same mechanism of action as ONTAK (BLA 103767), but is provided in a more purified form with a higher percentage of active monomer, resulting in higher potency product.

The product is proposed for the treatment of patients with relapsed or refractory stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy, to be given at 9 µg/kg/day IV over 60 minutes on Days 1 through 5 of a 21-day treatment cycle, to be administered until disease progression or unacceptable toxicity. Denileukin diftitox targets and binds to the CD25 component of the IL-2 receptor expressed on the CTCL cells and is internalized, where the Diphtheria toxin fragment is cleaved off the molecule and subsequently inhibits protein synthesis resulting in cell death. The potency of the product is measured using a cell-based anti-proliferation assay that utilizes the HH cell line, a human cutaneous T-cell lymphoma cell line. Cell death is measured by reduced fluorescence of the resorufin dye that is generated by viable cells upon incubation with resazurin dye.

Lymphir (Denileukin diftotox-cxdl) for injection, is a white, lyophilized sterile cake with a nominal content of 300 µg/vial of Denileukin diftotox supplied in a single use, clear glass vial with a (b) (4) rubber stopper and an aluminum seal. No preservatives are used in the formulation. The drug product is to be reconstituted in 2.1 mL of water for injection (WFI), resulting in a (b) (4) solution at the final concentration of 150 µg/mL. The resuspended drug product is to be further diluted in saline for intravenous use.

The Denileukin diftotox drug substance (DS) manufacturing process consists of production from *E. coli* (b) (4)

(b) (4)

The Drug product (DP) is produced using a standard (b) (4) manufacturing process which included (b) (4)

(b) (4)

During the original review cycle, several microbiology and product quality related deficiencies and additional comments were identified [refer to Complete Response Letter (CRL) issued to Citius Pharmaceuticals, Inc. on July 28, 2023].

The responses to the deficiencies and additional comments included in the CRL were adequately addressed in the BLA resubmission and provide overall assurance of the manufacture of a consistent, safe, pure and potent product, incorporating control over raw materials, facilities and equipment, the manufacturing process, microbial contamination, and release and stability of the drug substance and drug product. The new endotoxin assay using the EndoLISA d-rFC endotoxin testing method which was introduced in the resubmission was found acceptable for use as validated for the drug product release testing. Additional data were provided to support reference standard qualification and requalification, and in responses to the deficiencies the applicant provided updated quality agreements to assure that the applicant has sufficient knowledge of and direct control over the manufacturing process.

Post-marketing commitments to include validation and implementation for (b) (4)
(b) (4) and validation of the updated method for (b) (4)

Additional changes in criticality were made to specific manufacturing steps that provide higher assurance of (b) (4)
(b) (4) is pending in order to add assurance of a safe and pure product.

An inspection of the new endotoxin testing facility, (b) (4) (FEI # (b) (4)) for the proposed testing for endotoxin by a non-compendial assay, was found acceptable.

The assays used for immunogenicity assessment in the clinical studies to support this BLA were reviewed during the first review cycle and were found to be adequately validated and suitable for their intended purpose.

b. Subdiscipline Recommendation:

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

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deems acceptable.

d. Potency Assessment for Labeling:

As an initial matter, we determined that no U.S. standard of potency has been prescribed for Denileukin diftitox (i.e., there is no specific test method described in regulation for Denileukin diftitox that establishes an official standard of potency). We next considered whether potency is a factor for Denileukin diftitox 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 Lymphir for the purposes of § 610.61(r) because lot variability is not a concern for Lymphir as Lymphir'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:

(b) (4)

- Drug substance post approval annual stability protocol

ii. Residual risk:

- (b) (4)
(Refer to PMC).
- (b) (4)
(Refer to PMC).

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:

- Drug product post approval stability protocols and stability 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/

CHANA FUCHS
08/02/2024 02:53:09 PM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	July 23, 2024
Assessor:	Liming Lu, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Jee Chung, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XVI
Application:	BLA 761312
Applicant:	Citius Pharmaceuticals, Inc.
Submission Date:	February 13, 2024
Product:	Lymphir (denileukin diftitox-cxdl)
Dosage form(s):	For injection
Strength and Container-Closure:	300 mcg lyophilized cake in a single-dose vial
Purpose of assessment:	The Applicant re-submitted a biologics license application to address product quality deficiencies identified in the complete response letter received on July 28, 2023.
Recommendations:	The prescribing information, 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 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 (submitted on July 16, 2024), container labels (submitted on February 13, 2024), and carton labeling (submitted on June 25, 2024) were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on July 19, 2023)
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1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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), 21 CFR 600.3(k)	☒ 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

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

Comment/Recommendation: Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

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."

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, Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

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: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022) USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

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: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</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

Comment/Recommendation: The product does not need a Medication Guide. Thus, a Medication Guide statement is not required per 21 CFR 610.60(a)(7).
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No Package for container (container label)	Acceptable
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The container is enclosed in a package.

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

Comment/Recommendation: The product contains a container label.

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.

The applicant has confirmed there is no text on the ferrule and cap overseal of the vials during last review cycle.

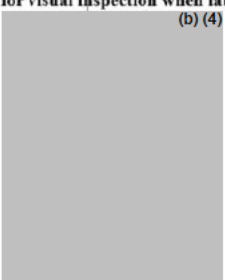
Visual inspection	Acceptable
Regulation: 21 CFR 610.60(e)	☒ Yes ☐ No ☐ N/A

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.

During last review cycle, the applicant has confirmed that a sufficient area of the vial remains uncovered for its full length to allow for visual inspection when the label is affixed to the vial, i.e., there is a (b) (4) gap between the label edges for visual inspection (Figure 1).

Figure 1 Representation of area for visual inspection when label is affixed to the vial

(b) (4)



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: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

No 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

Comment/Recommendation: The label does not display text in Spanish.
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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: The drug product does not contain FD&C Yellow No. 5 or 6.

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:</i> Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022)	☒ Yes ☐ No ☐ N/A

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references:</i> Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022) Guidance for Industry <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products</i> (June 2015) <i>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, FD&C Act section 502(e)	☐ 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
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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
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: During last review cycle, the applicant has revised to "Store Refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze." on the container label as requested.

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), 21 CFR 600.3(k)	☒ 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

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

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.

Comment/Recommendation: Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

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

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: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

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

Comment/Recommendation: During last review cycle, the applicant has revised to "Store Refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze." on the carton labeling as requested.

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

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

Route of administration (package labeling)	Acceptable
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	☒ Yes ☐ No ☐ N/A
<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

Comment/Recommendation: The container closure system is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

Inactive ingredients (package labeling)	Acceptable
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	☒ 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: During last review cycle, the applicant has revised the inactive ingredients list 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

Comment/Recommendation:
Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for **denileukin diftitox** products (i.e., there is no specific test method described in regulation for **denileukin diftitox** 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 **Lymphir** because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i>	☒ Yes ☐ No ☐ N/A

Divided manufacturing (package labeling)	Acceptable
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

Distributor (package labeling)	Acceptable
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	☐ Yes ☐ No ☒ N/A
Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Bar Code Label Requirements Questions and Answers</i> (August 2011) Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022)	☒ Yes ☐ No ☐ N/A
Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	Acceptable
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A
NDC numbers (package labeling)	Acceptable
Regulations: 21 CFR 201.2, 21 CFR 207.35	☒ Yes ☐ No ☐ N/A
Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> (May 2022) USP General Chapters <7> Labeling	☒ Yes ☐ No ☐ N/A
Package type term (package labeling)	Acceptable
Recommended labeling practices: Guidance for Industry <i>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</i> (October 2018) USP chapter <659> Packaging and Storage Requirements	☒ Yes ☐ No ☐ N/A
No 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

Comment/Recommendation: The label does not display text in Spanish.

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: The drug product does not contain FD&C Yellow No. 5 or 6.

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

Comment/Recommendation: The drug product does not contain phenylalanine.

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

Comment/Recommendation: The drug product does not contain sulfites.

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)</i> <i>Guidance for Industry Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)</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

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

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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A
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Comment/Recommendation: We revised to "lyophilized cake" based on the submitted specification sheet which specifies that lyophilized drug product is a white lyophilized cake.

The applicant has 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 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."</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; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components</i> <i>Draft Guidance Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2023)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: *The applicant has revised as requested during the last review cycle including a timeframe for a refrigerated item to reach room temperature, addition of the required verbatim for parenteral, revision of diluted drug product in-use storage information, and removal of (b) (4) from the section.*

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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to "lyophilized cake" based on the submitted specification sheet which specifies that lyophilized drug product is a white lyophilized cake.

The applicant has revised as requested.

Full Prescribing Information	
11 DESCRIPTION	Acceptable
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7></i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: We revised to "lyophilized cake" based on the submitted specification sheet which specifies that lyophilized drug product is a white lyophilized cake.

The applicant has revised as requested.

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

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

Comment/Recommendation: We revised to "lyophilized cake" based on the submitted specification sheet which specifies that lyophilized drug product is a white lyophilized cake.

The applicant has revised as requested.

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

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on July 16, 2024)
<\\CDSESUB1\EVSPROD\bla761312\0050\m1\us\114-labeling\114a-draft-label\11413-draft-labeling-text-clean.docx>
- Container Labels (submitted on February 13, 2024)
<\\CDSESUB1\EVSPROD\bla761312\0042\m1\us\114-labeling\114a-draft-label\11411-draft-labeling-text-clean.docx>

(b) (4)

- Carton Labeling (submitted on June 25, 2024)
<\\CDSESUB1\EVSPROD\bla761312\0047\m1\us\114-labeling\114a-draft-label\11411-draft-carton-labels-300mcg.pdf>

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



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Lu

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Jee
Chung

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BLA Executive Summary

Assessment Date: 7/26/2023

1. Application/Product Information

BLA number	761312
Submission Type	Original Submission
Regulatory Pathway	NME 351 (a)
Associated IND(s)/BLA	IND 110489; IND 004682; BLA 103767
Review Designation	Standard review
Applicant	Citius Pharmaceuticals, Inc.
Indication	For the treatment of adult patients with persistent or recurrent cutaneous T-cell lymphomas after at least 1 prior systemic therapy, (b) (4)
Rx/OTC dispensed	Rx
Drug Product Name	Lymphir
	(Denileukin diftitox-cxdl)
	FUS: RPROT P00587 (DTX_COROM) or P00588 (DTX_CORBE); RPROT P60568 (IL-2_HUMAN) [E7777]
Drug Product Description	LYMPHIR is supplied as a sterile, preservative-free, white, lyophilized cake in a single-dose vial. The nominal content of each vial is 300 mg of denileukin diftitox, (b) (4) mg trehalose dihydrate, 3.0 mg methionine, 1.2 mg polysorbate 20, 0.04 mg edetate disodium, 4.2 mg citric acid monohydrate. Sodium hydroxide is used to adjust the pH of the formulation buffer. The lyophilized DP is to be reconstituted with 2.1 mL of water for injection (WFI) to make a (b) (4) mL solution at 150 µg/mL denileukin diftitox concentration for further dilution prior to IV administration.
	Denileukin diftitox is a recombinant IL-2 directed cytotoxin cytotoxin made up of diphtheria toxin fragments A and B (Met ₁ -Thr ₃₈₇) fused to human interleukin 2 (Ala ₁ -Thr ₁₃₃) and produced (b) (4) in <i>E. coli</i> . (b) (4)

	(b) (4)		
Dosage Form	Lyophilized powder		
Strength	300 mcg/vial		
Route of Administration	Intravenous infusion		
Primary container closure system	Vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Subdiscipline	Primary	Secondary
	Drug substance	Jee Chung	Chana Fuchs
	Drug product	Jee Chung	Chana Fuchs
	Immunogenicity Assay	Jee Chung	Chana Fuchs
	Facility	DS - Charles Kuo DP -Chani Broner	Zhong Li
	Microbiology	DS - Charles Kuo DP -Chani Broner	Maxwell Van Tassell
	RBPM	Kristine Leahy	
	ATL	Chana Fuchs	

OPQ Issued Consults	Yu-Ting Weng; Meiyu Shen: OTS/OB/DBVI, immunogenicity assay statistical analysis.
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2. Recommendation and Conclusion on Approvability

Recommendation: Complete Response

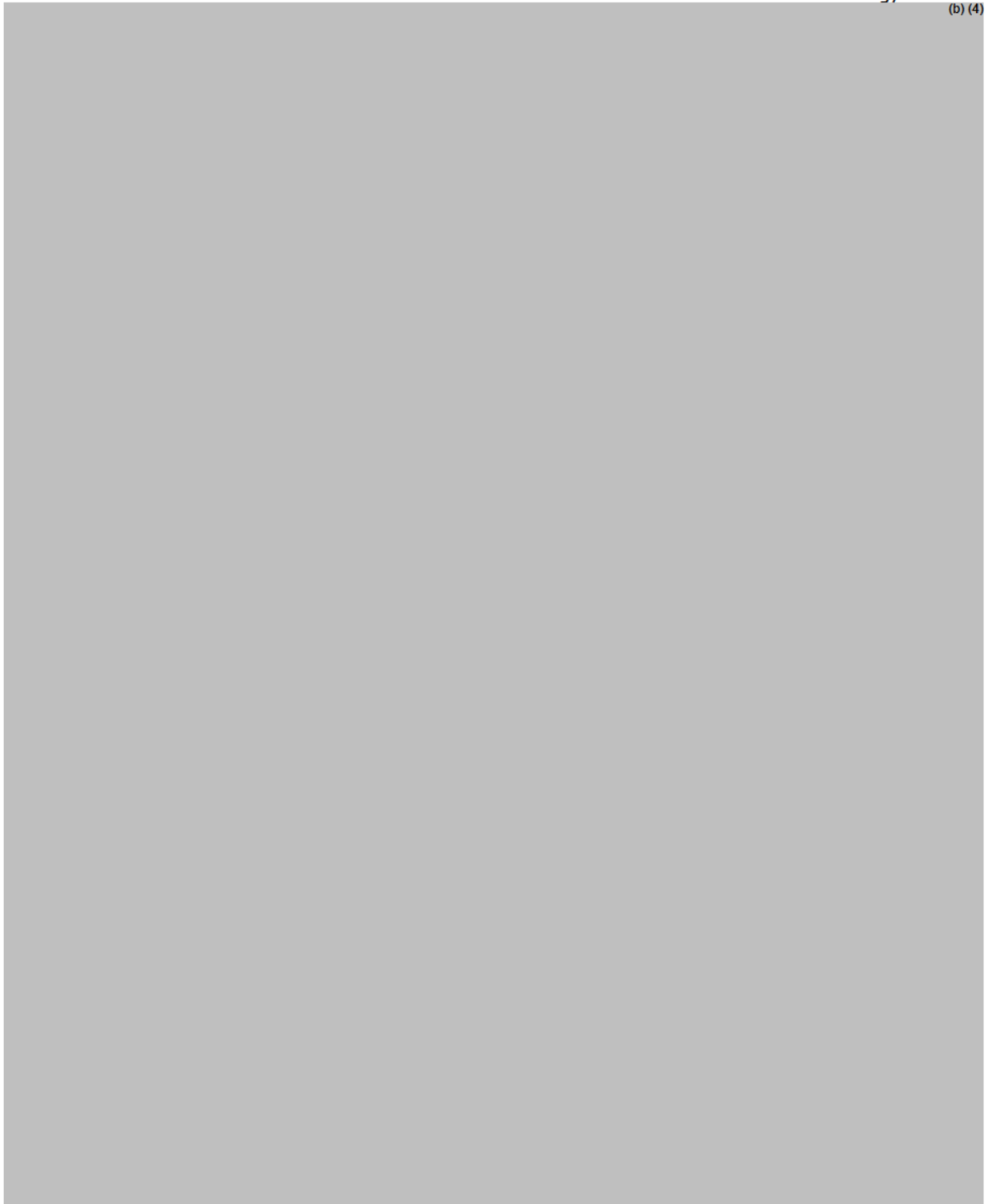
The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of BLA 761312 for Lymphir (Denileukin diftitox-cxdI) manufactured by Citius Pharmaceuticals, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of Lymphir is well-controlled and will lead to a product that is pure and potent. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Citius Pharmaceuticals, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

- a. Draft Complete Response Comments and Additional Comments, if applicable

Product Quality and microbiology Complete Response Comments

1)

(b) (4)



3. Basis for Recommendation

a. Summary:

Denileukin diftotox (development code E7777) is a recombinant fusion protein consisting of diphtheria toxin fragments A and B fused to human interleukin 2. It is produced (b) (4)

(b) (4) in *E. coli* (b) (4) (b) (4)

(b) (4)

Denileukin diftitox has the same sequence and the same mechanism of action as ONTAK (BLA 103767), but is provided in a more purified form with a higher percentage of active monomer, resulting in higher potency product.

The product is proposed for the treatment of patients with relapsed or refractory stage I-III cutaneous T-cell lymphoma (CTCL) after at least one prior systemic therapy, to be given at 9 µg/kg/day IV over 60 minutes on Days 1 through 5 of a 21-day treatment cycle, to be administered until disease progression or unacceptable toxicity. Denileukin diftitox targets and bind to the CD25 component of the IL-2 receptor expressed on the CTCL cells and is internalized, where the Diphtheria fragment is cleaved off the molecule and subsequently inhibits protein synthesis resulting in cell death. The potency of the product is measured using a cell-based anti-proliferation assay that utilizes the HH cell line, a human cutaneous T-cell lymphoma cell line. Cell death is measured by reduced fluorescence of the resorufin dye that is generated by viable cells upon incubation with resazurin dye.

Lymphir, Denileukin diftitox for injection, is a white, lyophilized sterile cake with a nominal content of 300 µg/vial of E7777 supplied in a single use, clear glass vial with a (b) (4) rubber stopper and an aluminum seal. No preservatives are used in the formulation. The drug product is to be reconstituted in 2.1 mL of WFI, resulting in a (b) (4) solution at the final concentration of 150 µg/mL. The resuspended drug product is to be further diluted in saline for intravenous use.

Denileukin diftitox drug substance (DS) manufacturing process consists of production from *E. coli*

(b) (4)

(b) (4)

The Drug product (DP) is produced using a standard (b) (4) manufacturing process which included (b) (4)

(b) (4)

The overall manufacturing control strategy incorporates control over raw materials, facilities and equipment, the manufacturing process, microbial contamination, and release and stability of the drug substance and drug product. However, multiple deficiencies were identified and cannot be adequately addressed during the assessment period, including:

- There is no appropriate assay for endotoxin level measurement and lack of controls for endotoxin testing on (b) (4) the drug substance (DS) and drug product (DP) (b) (4).
(b) (4) all data on assay capabilities and validation of these assays were not available during the BLA review timeline.
- There is a lack of information to show that the applicant has sufficient knowledge of and direct control over the manufacturing process. (b) (4) however, these activities are not going to be completed during the BLA review timeline.
- There are insufficient sterilization validation data for contact materials used in DP manufacturing, additional data would be required to complete the validation process.
- There are insufficient data to support adequacy of the DS bioburden control strategy and the bioburden method. Additional data would be required to complete the validation process.
- There are insufficient data to support the Reference Standard qualification and requalification protocols. Data to support the requalification/stability ranges of the primary and working reference standards would be required prior to approval.
- There are insufficient data for validation of the DP batch range. These data would be required, (b) (4), prior to approval.

In addition, an inspection of the (b) (4) (FEI # (b) (4), (b) (4)) facility, the site for the proposed testing for endotoxin by the non-compendial assay, will be required before this application can be approved. FDA must assess the ability of this facility to conduct the listed manufacturing operations in compliance with CGMP. Due to the timing of incorporation of the site into the license application, FDA was unable to conduct an inspection during the current application review cycle.

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

b. Subdiscipline Recommendation:

Drug Substance	-	Inadequate
Drug Product	-	Inadequate
Immunogenicity Assay	-	Adequate
Facilities	-	Pending

Microbiology - Inadequate

c. Environmental Assessment (EA):

Categorical exclusion is claimed by the applicant and deems acceptable.

d. Potency Assessment for Labeling:

Not applicable as OPQ does not recommend approval of this application.

4. Life-Cycle Considerations

Not applicable as OPQ does not recommend approval of this application.

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/

CHANA FUCHS
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JENNIFER F SWISHER
07/27/2023 11:25:19 PM

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

Application ID	BLA 761312/0
Submission Type	Original BLA
Drug Product Name	Denileukin diftitox (E7777)
Strengths	300 mcg/vial
Dosage Form	Injection; Lyophilized powder, sterile solution
Administration Route	Intravenous
Indication	Cutaneous T-cell Lymphoma
Applicant Name	Citius Pharmaceuticals, Inc.
US License Number	2290
Application Type	351 (a)
Primary Reviewer	Charles Yuan-Chia Kuo, Ph.D., Reviewer, OPQ/OPMA/DBM/B1
Secondary Reviewer	Maxwell Van Tassell, Ph.D., SPQA, OPQ/OPMA/DBM/Branch 1 (Microbiology) Zhong Li, Ph.D., SPQA, OPQ/OPMA/DBM/Branch 1 (Facility)
Goal Date	28-July-2023

Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and is NOT recommended for approval. The following deficiencies should be included in the Complete Response Letter:

1)

(b) (4)

2)

- The following additional comment should be included in the Complete Response Letter:

(b) (4)

○

○

- Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DS):

Microbial quality is controlled

(b) (4)

4)

(4)

however the lack of available validated method for detection of endotoxin
(b) (4) has led to no data that can support the clearance of endogenous
endotoxin from the product.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and cross-contamination control strategy were provided for (b) (4)
(b) (4) (FEI (b) (4)), proposed for Denileukin diftitox (E7777) DS manufacture. All proposed DS manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Pyrogen	Safety, Purity	Raw materials, manufacturing process	(b) (4)	
Bioburden	Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination	Raw materials, manufacturing process		

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
Original Submission/SN0001	9/28/2022
Response to Information Request/SN0007	12/14/2022
Response to Information Request/SN0013	2/21/2023
Response to Information Request/SN0020	4/14/2023
Response to Information Request/SN0024	5/12/2023
Response to Information Request/SN0029	6/12/2023
Response to Information Request/SN0030	6/20/2023
Response to Information Request/SN0033	6/27/2023

Application Submission Background

Reviewer's Comment: For Information

Citius Pharmaceuticals, Inc. submits Biologics License Application (BLA) for E7777 which has the same active drug substance, denileukin diftitox, and the same mechanism of action as ONTAK (BLA 103767). Denileukin diftitox has direct cytotoxic activity against the IL-2 receptor (of which CD25 is a subunit) to treat patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) (b) (4)

(b) (4). E7777 has an improved purity profile and greater potency as a result of higher active monomer content relative to ONTAK. E7777 is produced using an improved manufacturing process for denileukin diftitox (b) (4)

The responses of Information Request regarding low endotoxin recovery (LER) and development of endotoxin detection method are summarized under section 3.2.S.2.4.

MODULE 3.2.S

Module 3.2.S Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

S.1 General Information

Denileukin diftitox was originally approved for marketing in the US under the tradename Ontak by Eisai. The E7777 DS development process in (b) (4) site, referred to as Process B, modified the Ontak manufacturing process (b) (4)

(b) (4) The bioactivity of E7777 demonstrates an increase of in vitro activity achieved with the improved manufacturing process. Eisai transferred production of E7777 Process B from the

(b) (4) site to (b) (4) referred as Process C, with formulation modification to support lyophilized presentation of the drug product, and later optimized to Process D as final commercial process in 2019. Eisai withdrew Ontak from the market in 2014 due to production issues related to bacterial expression and purification challenges. In September 2021, Citius acquired an exclusive license to develop and commercialize a late-stage cancer immunotherapy to replace Ontak from Dr. Reddy's Laboratories SA (in association with Eisai Co. Ltd).

Reviewer's Comment: For Information

S.2 Manufacture

S.2.1 Manufacturer(s)

(b) (4)

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Charles Yuan-
Chia
Kuo

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Maxwell
Van Tassell

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Christopher
Downey

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

Application ID	BLA 761312
Submission Type	Original BLA
Drug Product Name	Denileukin diftitox
Strengths	300 mcg/vial
Dosage Form	Injection; Lyophilized powder, sterile solution
Administration Route	Intravenous
Indication	Cutaneous T-cell Lymphoma
Applicant Name	Citius Pharmaceuticals, Inc.
US License Number	2290
Application Type	351 (a)
Primary Reviewer	Esther C. Broner, PhD, Pharmaceutical Scientist, OPMA/DBM/B1
Secondary Reviewer	Maxwell Van Tassell, PhD, SPQA, OPMA/DBM/B1
Secondary Facility Reviewer	Zhong Li, PhD, SPQA, OPMA/DBM/B1
Goal Date	7/28/2023

Recommendation for Approvability:

- This BLA was reviewed from a sterility assurance perspective and is NOT recommended for approval. The following deficiencies should be included in the Complete Response Letter:

1) [REDACTED] (b) (4)

(b) (4)

The following Additional Comments should be included in the Complete Response Letter:

An inspection of the (b) (4) (FEI # (b) (4) facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to the timing of incorporation of the site into the license application, we were unable to conduct an inspection during the current review cycle for your application

- Manufacturing Facility Assessment Recommendation: Withhold
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

Summary Basis of Recommendation (DP):

The drug product is sterilized

(b) (4) However, no method has been successfully validated to detect endotoxin (b) (4) An alternative endotoxin method has been proposed to be validated in coming months and implemented at a testing site added to the license application too late in the review cycle to evaluate the facility, which has no FDA inspection history. Container closure integrity testing using a validated method is included in the stability program.

Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (Contaminant)	Safety, Purity, and Efficacy	Manufacturing process, failure of the container closure integrity	(b) (4)	

			(b) (4)	
Endotoxin (Contaminant)	Safety, Purity	Raw materials, manufacturing process		This method is not validated.
Endotoxin (Contaminant)	Safety, Purity	Raw materials, manufacturing process		(b) (4)
Container closure integrity (Sterility assurance)	Safety (Sterility assurance)	Breach during manufacture or storage		

List of Submissions Assessed (Table):

Document Description (Sequence #)	Date Received
BLA Original Submission (SN0001)	9/28/2022
IR response – Microbial Attributes (SN0015)	3/16/2023
IR Response – LER (SN0013)	02/21/2023
IR Response – LER (SN0020)	04/14/2023
IR Response – LER (SN0024)	5/12/2023
IR Response – LER (SN0029)	06/12/2023
IR Response – LER (SN0030)	6/20/2023
IR Response – LER (SN0033)	06/27/2023
IR Response (SN0034)	6/29/2023

List of DMFs Assessed (Table):

DMF #	Item Referenced	Date Reviewed	Finding	Document Reference
(b) (4)		7/22/2021	Adequate	D (b) (4) M56R01.docx

Application Submission Background

Citius Pharmaceuticals, Inc. has submitted this Biologics License Application (BLA) for Denileukin difitox for the treatment of patients Cutaneous T-cell Lymphoma, a rare disease with an FDA Orphan Designation.

Reviewer's Comment: For Information

MODULE 1

1.14 LABELING

Reconstitution and Dilution Instructions

IR #1 03/10/2023

Microbiological studies in support of the post-dilution storage time of (b) (4) hours at 20°C to 25°C as stated in the proposed product labeling have not been provided. Please provide a risk assessment summarizing studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions [(i.e., (b) (4) hours at approximately 20°C to 25°C). Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Please include a description of the test methods and results of studies that are designed using a minimum countable inoculum (<100 CFU/mL) to simulate potential microbial contamination that may occur during product constitution or dilution. It is generally accepted that growth is evident when the population increases more than 0.5 log₁₀, however other evidence of growth may be significant. Please perform the test using the storage conditions (temperature and duration) and diluents specified in product labeling. Please provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the reconstituted or diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms should include strains described in USP <51> and may include additional organisms based on appropriate scientific rationale. Please provide a positive control that demonstrates the viability of the organisms at the start of the study. The RLD may be tested in parallel to demonstrate equivalence.

Summary of Applicant's Response (SN0015):

The Applicant has agreed to modify the post dilution storage conditions to no more than 4 hours at 20-25 °C.

Reviewer's Comment: For Information

MODULE 3.2.P

Module 3.2.P Lifecycle Management Considerations

Lifecycle considerations:	No
Post-approval inspection?	No

P.1 Description and Composition of the Drug Product

Denileukin diftitox (E7777) for injection is a white, lyophilized sterile cake with a nominal content of 300 µg/vial of E7777 supplied in a single use, clear glass vial with a (b) (4) rubber stopper and an aluminum seal. DP is to be reconstituted in 2.1 mL of WFI, resulting in a (b) (4) solution at the final concentration of 150 µg/mL. DP is further diluted in saline for intravenous use. DP contains no preservatives. The composition of DP is detailed in the table below (Table 3.2.P.1-1):

Table 3.2.P.1-1 Components and Composition of E7777 for Injection

Components ^a	Nominal amount per vial	Actual Amount per Vial ^b	Function	Specification
denileukin diftitox	300 µg	(b) (4)	Active Ingredient	In-house
Trehalose ^c	100.4 mg	(b) (4)		NF, Ph. Eur.
Methionine	3.0 mg	(b) (4)		USP, Ph. Eur.
Polysorbate 20	1.2 mg	(b) (4)		NF, Ph. Eur.
Edetate Disodium ^d	0.04 mg	(b) (4)		USP, Ph. Eur.
Citric Acid ^e	(b) (4)	4.2 mg		USP, Ph. Eur.
Sodium Hydroxide	q.s.	q.s.	Alkalizing Agent	NF, Ph. Eur.
Water for Injection ^f	(b) (4)	(b) (4)		USP, Ph. Eur.
	(b) (4)	(b) (4)		NF, Ph. Eur.

NF = National Formulary (US), Ph. Eur. = European Pharmacopoeia, USP = U.S. Pharmacopeia, q.s. = *quantum sufficit* stands for sufficient quantity.

a: Names as listed in USP/NF.

b: (b) (4) of the indicated or labeled amount is overfilled to ensure that 300 µg of E7777 can be withdrawn from a vial.

c: 100.4 mg of trehalose provided (b) (4)

d: 0.04 mg of edetate disodium provided by (b) (4)

e: (b) (4) 4.2 mg of citric acid monohydrate.

f: (b) (4)

Reviewer's Comment: For Information Only

P.2 Pharmaceutical Development

Container Closure Integrity Testing

See section P.5.2 and P.5.3

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BLA STN 761312
Lymphir (Denileukin diftitox-cxdl)
Citius Pharmaceuticals, Inc.

OBP Product Quality Assessment Data Sheet

1. BLA#: 761312
2. Assessment Date: 10/1/2022
3. Primary Assessment Team:
 - a. Medical Officer: Shyamli Singla
 - b. Pharm/Tox: Moran Choe
 - c. Product Quality Team: Jee Chung
 - d. Facilities and Microbiology: Charles Yuan-Chia Kuo/Chani Broner
 - e. Clinical Pharmacology: Francis Green
 - f. Statistics: Sarabdeep Singh
 - g. OBP Labeling: Liming Lu
 - h. RBPM: Kristine Leahy
 - i. RPM: Ashlee Bow
4. Major GRMP Deadlines:
 - a. Filing Meeting: 11/27/2022
 - b. Mid-cycle meeting: 2/22/2023
 - c. Wrap-up meeting: 7/11/2023
 - d. Primary review due: 5/28/2023
 - e. Secondary review due: 6/11/2023
 - f. PDUFA action date: 7/28/2023

5. Communications with Sponsor and OND:

Communication/Document:	Date:
IR1: OPMA Manufacturing Schedule	10/12/2022
IR2: OPMA Manufacturing Schedule	11/1/2022
IR3: OBP	11/30/2022
IR4: OPMA	2/8/2023
IR5: OBP	3/10/2023
IR6: OBP and OPMA	3/24/2023
IR7: Immunogenicity IRs	4/20/2023
IR8: OBP	5/9/2023
IR9: OBP	5/25/2023
IR10: OPMA	6/2/2023
IR11: OBP Immunogenicity	6/12/2023
IR12: OBP method and DS	6/14/2023
IR13: OPMA	6/15/2023
IR14: Immunogenicity	6/28/2023
IR15: OBP Spec	6/30/2023
IR16: Immunogenicity email	7/6/2023

6. Submission Assessed:

Submission:	Date Received:	Assessment Completed (yes or no)
0002/2: IR1 Response	10/17/2022	yes

003/3: IR2 Response	11/14/2022	yes
0007/7: IR3 Response	12/14/2022	yes
0012/12: IR3 Response follow-up	2/15/2023	Yes-DP filling strategy
0013/13: IR4 Response OPMA	2/21/2023	OPMA-rabbit pyrogen testing (yes)
0015/15: IR5 Response OBP/OPMA label	3/16/2023	yes
0018/18: Response IR6 OBP	4/7/2023	yes
0021/21: Response IR7 OBP Immunogenicity	5/1/2023	yes
0024/24: OPMA	5/12/2023	OPMA (yes)
0025/25: OBP	5/16/2023	yes
0026/26: OBP Labeling	5/30/2023	Labeling (yes)
0027/27: OBP	6/5/2023	DS process; yes
0029/29: OPMA	6/12/2023	OPMA (yes)
0030/30: OPMA	6/19/2023	OPMA Endotoxin (yes)
0031/31: OBP Immuno	6/20/2023	yes
0032/32: OBP DS	6/21/2023	yes
0033/33: OPMA	6/27/2023	OPMA (yes)
0034/34: OPMA		
Email response/clarification	6/30/2023	yes
0035/35: Immunogenicity IR response	7/6/2023	Clinical pharmacology immunogenicity data reassessment summary
0036/36: OBP Spec	7/7/2023	yes

7. Drug Product Name/Code/Type:

- a) Proprietary Name: Lymphir
- b) Trade Name: lymphir
- c) Non-Proprietary Name/USAN: Denileukin diftiox-cxdl
- d) CAS Name: 173146-27-5
- e) Common Name: E7777
- f) INN Name: Denileukin diftiox
- g) Compendial Name: N/A
- h) OBP systematic name: FUS: RPROT P00587 (DTX_COROM) or P00588 (DTX_CORBE); RPROT P60568 (IL-2_HUMAN) [E7777]

8. Pharmacological Category: IL-2 directed cytotoxin

9. Dosage Form: Injection, powder, lyophilized. For solution

10. Strength/Potency:

- i. Strength: 300 mcg/vial
- ii. Potency: cell-based anti-proliferation assay that utilizes human cutaneous T-cell lymphoma cell line, HH cells. Exposure to E7777 leads to internalization of E7777 mediated through binding to

cell surface expressed IL-2 receptor and release of the diphtheria toxin into the cytoplasm to inhibit protein synthesis and induce cell death.

11. Route of Administration: Intravenous infusion

12. Referenced Drug Master Files (DMF):

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
		(b) (4)	Provided in the BLA	Sufficient leachables and extractables and primary stability data in the BLA
			Provided in the BLA	Sufficient leachables and extractables and primary stability data in the BLA
			Provided in the BLA	Defer to OPMA
			Provided in the BLA	Sufficient leachables and extractables and primary stability data in the BLA
			Provided in the BLA	Sufficient leachables and extractables and primary stability data in the BLA; Closure is not made with Natural Rubber Latex or Dry Natural Rubber; (b) (4) review is deferred to OPMA

13. Inspectional Activities:

A pre-license inspection of the drug substance manufacturing facility at (b) (4) (FEI (b) (4) (b) (4)) was conducted on (b) (4) by Patricia Hughes, Xiaoxiao Pan, and Jee Chung. The inspection covered the drug substance manufacturing process, including Quality, Facilities and Equipment, Production, Materials, and Laboratories CGMP systems related to the E7777 drug substance, and assessment of compliance with the standards established in the BLA and in the regulations. The issues identified related to (b) (4) (b) (4)

Inspection of the drug product manufacturing facility, (b) (4), (b) (4) (FEI: (b) (4)) was waived based on the firm's compliance history, current acceptable cGMP status and the similar (b) (4) manufacturing process of other licensed products in the same fill area/line.

An inspection of the (b) (4) (FEI # (b) (4)) facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to the timing of incorporation of the site into the license application, FDA was unable to conduct an inspection during the current review cycle for your application.

14. Consults Requested by OBP: Meiyu Shen and Yu-Ting Weng (CDER/OTS/OB/DBV) for statistics evaluation of immunogenicity assay cut-points.

15. Quality by Design Elements:

The following was submitted in the identification of QbD elements (check any that apply):

	Design Space
x	Design of Experiments
x	Formal Risk Assessment/Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. Precedents: None

17. Administrative:

Summary of Quality Assessments

I. Primary Assessor Summary Recommendation

The data submitted in this Biologic License Application are not adequate to support the conclusion that the manufacture of denileukin diftotox-cxdl is well controlled and leads to a product that is pure and potent.

II. List of Deficiencies to be Communicated (from OBP and OPMA)

1) (b) (4)

8)

(b) (4)

Additional CMC Comments (non-approvability issues from OBP and OPMA):

1)

(b) (4)

2)

3)

III. List of Post-Marketing Commitments/Requirements: N/A

IV. List of Protocols (protocols currently in the BLA)

eCTD Section	Protocol	Brief Summary	Reporting Category
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3.2.S.2.3	(b) (4)	PAS
3.2.S.5		Approved
3.2.S.7.2		Approved
3.2.P.8.2		Approved

- V. Assessment of Common Technical Document- Quality Module 1
A. Environmental Assessment of Claim of Categorical Exclusion
Citius Pharmaceuticals, Inc. claims a Categorical Exclusion from the environmental assessment requirements for E7777 under 21 CFR Part 25.31(b).

- VI. Primary Container Labeling Assessment
A separate primary container labeling review was performed by Liming Lu, OBP.

VII. Assessment of Common Technical Document- Quality Module 3.2

CQA	DS, DP, or both	Risk	Origin	Control Strategy	Other
Identity					
Unique epitopes generated by sequence detected by antibodies	Both	Impact on safety and efficacy	Intrinsic to molecule	(b) (4)	
Unique peptide fragments that are generated based on sequence	DS	Impact on safety and efficacy	Intrinsic to molecule		(b) (4)
Biological Activity					
Potency (by Cell-based assay)	Both	Impact on safety and efficacy	Intrinsic to the molecule. Impacted by conditions (b) (4) and storage (stability)	(b) (4)	(b) (4)

					(b) (4)
General Property					
Appearance-DS and re-constituted DP (Color, Clarity) by visual inspection	Both	Safety	Manufacturing process and formulation	(b) (4)	(b) (4)
Appearance-lyophilized	DP	Safety	Manufacturing process and formulation		
Appearance Visible Particulate Matter	DP	Safety and immunogenicity	DS and DP Manufacturing processes, formulation, interaction with the container closure system		
Subvisible Particulate Matter (product or process related impurities)	DP	Safety and immunogenicity	Manufacturing process (product and contact material) and container closure system. Could be product or foreign particles.		
Reconstitution Time	DP	Efficacy	Formulation components		
(b) (4)	DP	Safety and Efficacy (product quality) through expiration dating.	Manufacturing process and container closure system (CCS)		
Uniformity of dosage unit	DP	Efficacy	Manufacturing process (b) (4) and (b) (4) filling step		
Deliverable volume	DP	Efficacy/dosing	DP manufacturing process		
pH	Both	Safety and efficacy	Formulation manufacturing process		

(b) (4)	Both	Safety and efficacy	Formulation manufacturing process	(b) (4)	(b) (4)
(b) (4)	Both	Safety and efficacy	Formulation manufacturing process		
Osmolality	DS	Safety and efficacy	Formulation manufacturing process		
Protein Concentration	Both	Safety and efficacy	(b) (4)		
Gross Content	DP	Safety and efficacy	DP manufacturing process		
Product Variant					
Impurities Peaks (b) (4) and other unknowns; Total impurities by RP-UPLC	Both	Efficacy	E7777 degradation during manufacturing and storage	(b) (4)	(b) (4)
Impurity Peak (b) (4) by RP-HPLC	DS	Efficacy	(b) (4); manufacturing and storage		
Impurity (b) (4) by Bioanalyzer	Both	Safety and immunogenicity	Manufacturing process and storage		
Impurity LMW species	Both	Safety and efficacy	Manufacturing process and storage		
Impurity Acidic peaks by IE-HPLC	Both	Efficacy	Fermentation, purification process; storage		

				(b) (4)	
Basic peaks by IE-HPLC	Both	Efficacy	Fermentation, purification process; storage		
N-terminal variants by HPLC/MS	DS	Efficacy	Fermentation, purification process; storage		
Impurity Oxidized species (b) (4) by RP-UPLC and RP-HPCL	Both	Efficacy	Manufacturing process and storage		
Deamidated species	Both	Efficacy	Manufacturing process and storage		
Process-Related Impurity					
Host cell protein by ELISA	DS	Safety, Immunogenicity	Process-related impurity from the production cell line.	(b) (4)	
Host cell DNA by qPCR	DS	Safety	Process-related impurity from the production cell line		
(b) (4)	DS	Safety	(b) (4) process		(b) (4)
	DS	Safety	Process-related impurity from (b) (4)		
	DS	Safety	Process-related impurity from (b) (4)		

(b) (4)	DS	Safety	Process-related impurity (b) (4)	(b) (4)
	DS	Safety	(b) (4)	
	DS	Safety	Process-related impurity (b) (4)	
	DS	Safety	Process-related impurity (b) (4)	
	DS	Safety	Process-related impurity (b) (4)	
Contaminant				
Microbial contaminants: bioburden	Both	Safety		(b) (4)
Microbial contaminants: sterility	DP	Safety	Manufacturing process or failure of container closure integrity	
Endotoxin	Both	Safety	Fermentation process, raw materials, manufacturing process or failure of container closure integrity (b) (4)	Complete response
Non-host	DS	Safety		

VIII. Assessment of Immunogenicity Assays- Module 5.3.1.4

A review of the immunogenicity assays is included at the end of the Technical Report.

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