



CMC Review Memorandum

Concurrence: I concur with this review. Laura Ricles, Ph.D. September 6, 2022.

Reviewer: Carolina Panico

BLA # 125755

Subject: Container Closure Review

Applicant: BlueBird Bio Inc.

Device Name: (b) (4)

Classification: Unclassified

Product Code: LPZ

Consult Requestor(s): Gene Therapy
Branch: Anna Kwilas, Jakob Reiser, Tal
Salz

Drug Product(s) Name: Elivaldogene
autotemcel

Request Date: March 23, 2022

Completion Date: September 6, 2022

Recommendation

I recommend that the (b) (4) testing and the visual inspection after (b) (4) be post-marketing commitments (PMCs), whereas the leachable and extractable assessments and toxicological risk assessment (TRA) be post-marketing requirements (PMRs).

(b) (4) Testing PMC

bluebird bio, Inc., commits to conducting (b) (4) testing following the conditions outlined in (b) (4) and provide justifications for the test method, results, and conclusions as part of a complete test report. Complete test reports for this (b) (4) testing on the (b) (4) bag will be submitted as a final study report by December 31, 2022, (Amendment 93, August 17, 2022).

(b) (4) Study PMC

bluebird bio, Inc., commits to perform a (b) (4) study to evaluate drug product bag integrity following (b) (4)

. Complete test reports for this testing

will be submitted as a final study report by December 31, 2022 (Amendment 93, August 17, 2022).

Leachables and Extractable Studies and related Toxicological Risk Assessment Postmarketing Requirements (PMR)

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of patient exposure to any unknown extractables and leachables, at this time, from the (b) (4) bag, in association with the use of elivaldogene autotemcel.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that the Applicant is required to conduct the following PMR studies. bluebird bio acknowledges and agrees with the (b) (4) PMR milestones and timelines language provided for BLA 125755 (Amendment 96, August 19, 2022):

1. A study to support the extractable data provided for the (b) (4) bag, including the sample processing steps in the (b) (4) and an appropriate identification process used for the extractables.
Draft Protocol Submission: August 31, 2022
Final Protocol Submission: November 30, 2022
Study Completion: February 28, 2023
Final Study Report Submission: April 30, 2023
2. A study to evaluate leachables of the (b) (4) bag over the duration of the shelf life of elivaldogene autotemcel. This evaluation will also include a full toxicological risk assessment for the identified leachables and extractables.
Draft Protocol Submission: August 31, 2022
Final Protocol Submission: November 30, 2022
Study Completion: January 30, 2024
Final Study Report Submission: March 30, 2024

The Applicant was requested to submit the protocols to the parent IND 15433, with a cross-reference letter to this BLA, STN BL 125755/0 explaining that these protocols were submitted to the IND.

Review Summary

This review was requested by the Gene Therapy Branch (GTB) to assess the suitability of the container closure (b) (4) for the drug product subject of BLA125717.

Therefore, the purpose of this review was to assess the safety and effectiveness of the (b) (4) when used as container closure for the drug product Elivaldogene autotemcel (eli-cel).

Document provided by the consult requestor

1. 3.2.P.7 Container Closure System.pdf
2. 3.2.P.2.4 - Container Closure System
3. Report# VAL-VEN-RPT-0127 ('Extractables Simulation Study for Final Drug Product in Contact with (b) (4) Ctyopreservation Bag and (b) (4) in Contact with (b) (4) ; dated June 6, 2018)

Document provided by the Applicant (April 29, 2022, and May 20, 2022) upon our request and reviewed in addition to those listed in 1-4 above and the information requests responses provided during the review:

4. (b) (4) -memo
5. (b) (4) -product-overview.pdf
6. packaging-performance-stability-validation-summary.pdf
7. technical-dossier-rev-c.pdf
8. validation-guide-summary.pdf
9. Reports numbers# pi-3020, pi-3163, vrtm-119, vrtm-407, vrtm-1008, vrtm-1101 (related to extractables and leachables information).

Executive Summary

The Applicant provided shelf life (the Applicant agreed to shorten the shelf life based on the current available data), shipping/packaging data, biocompatibility, endotoxin and most of the relevant testing (suspension hanger eyelet, (b) (4) testing) needed to show that the (b) (4) is safe and effective when used as intended for the purpose of this BLA. However, the leachables and extractables studies, the toxicological risk assessment (TRA), the (b) (4) and the integrity testing after (b) (4) are either deficient (extractable testing, TRA assessment) or missing (leachable testing, (b) (4) testing, integrity/visual inspection after (b) (4)). Therefore, the (b) (4) testing and the visual inspection after (b) (4) have been requested as post-marketing commitments (PMCs). The leachable, extractable testing and TRA have been requested as post-marketing requirements (PMRs).

Review Team

Lead Reviewer	Carolina Panico (CBER/OTAT/DCGT/TEB)
Team Leader	Alyssa Kitchel (CBER/OTAT/DCGT/TEB)
Scientific Reviewer	Bao-Ngoc Nguyen (CBER/OTAT/DCGT/TEB)
Toxicological Risk Assessment Consultant	Caroline Pinto (CDRH/OSEL/DBCMS)
Chemical Characterization Consultant	Felix (Zhaobo) Fan (CDRH/OSEL/DBCMS)

I. Purpose and History

In response to our information request from April 6, 2022, the Applicant, Bluebird Bio, stated (response from April 29, 2022) that (b) (4), the company that initially manufactured the (b) (4) (including the (b) (4) and (b) (4) product lines, had filed 510(k)s and Device Master Files for these product lines. The current manufacturer, (b) (4), subsequently withdrew the filings associated with these product lines and, in 2017, requested input on the regulatory requirements applicable to the (b) (4) bags through a 513g request (b) (4) summarized FDA's response that recommended that the (b) (4) bag be reviewed as part of BLAs for the cell therapy products and not as standalone devices.

In the letter, FDA stated that when used by cell product manufacturer as "single-use container-closure system and infusion reservoirs for cellular therapy products during their storage, preservation (including cryopreservation), and transportation up to the patient bedside", the (b) (4) Bag and the (b) (4) Bag would be reviewed as part of the BLA for the cell therapy not a standalone device. However, when distributed to Centers, and Cancer Centers, for the same intended use, depending on the type of product the bags will be used with, the (b) (4) Bag and the (b) (4) Bag may be reviewed as a standalone medical device under the following classification regulations and product codes:

1. For storage or preservation of certain cell types (e.g., hematopoietic progenitor cells):
Regulation Number: Unclassified
Regulation Name: Unclassified
Regulatory Class: Unclassified
Product Code: LPZ
Common Name: Container, frozen donor tissue storage
2. For storage or preservation of blood components:
Regulation Number: 21 CFR 864.9100
Regulation Name: Empty container for the collection and processing of blood and blood components
Regulatory Class: Class II
Product Code: KSR

Common Name: Container, empty, for collection & processing of blood and blood components

II. Container Closure Description

The container closure system proposed in BLA 125717 consists of a primary package container, the (b) (4) Cryopreservation bag (subject of this review), a secondary package container ((b) (4) Overwrap bag), and a tertiary package container (cryocassette).

The primary container closure, subject of this review, is a 20-mL fluorinated ethylene propylene (FEP) cryopreservation bag with maximum fill volume of (b) (4). The (b) (4) is manufactured by (b) (4).

Please see Table 1 and Figure 1 below (from 3.2.P.7 Container Closure System, page 3) for the specifications and representative drawings of the (b) (4)

Table 1: Specifications/Technical Information for (b) (4) Bag

Bag material	(b) (4)
Spike port with septum, protected with FEP cover	
Inlet tubing	
Female Luer	
Pinch clamp	
Inside bag dimensions	
Outside bag dimensions (including port and label pouch)	
Working temperature	

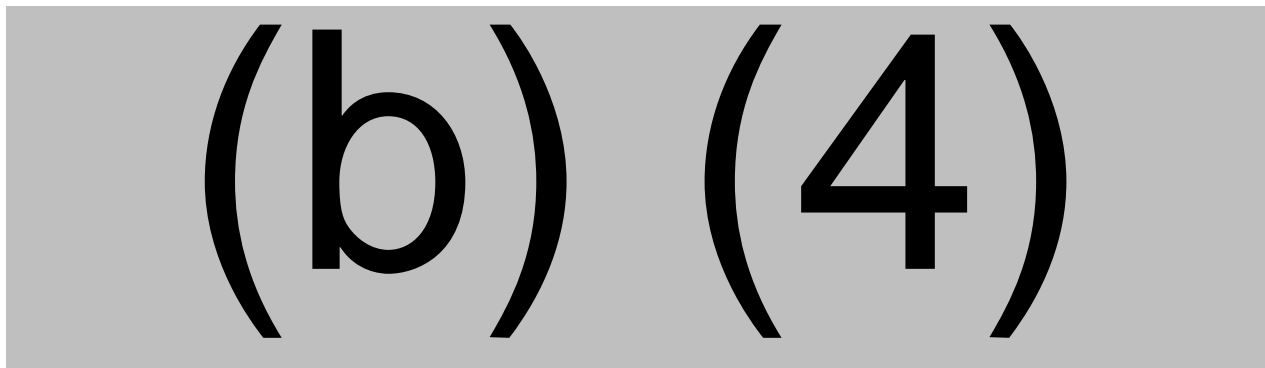
(b) (4)

Figure 1: Representative Drawing of (b) (4) Bag¹



In document 3.2.P.7, Container Closure System, the Applicant stated that the FEP (b) (4) used to manufacture the (b) (4) contains no additives, plasticizers, or slip agents, and is free of animal-derived components and has high oxygen permeability, low water vapor permeability, and a broad service temperature range.

Please see below extracts from document (b) (4) -product-overview.pdf' for the (b) (4) ports and tubing details and the size specifications.



(b) (4)

Reviewer Recommendation

The container closure description is acceptable.

Additional Information

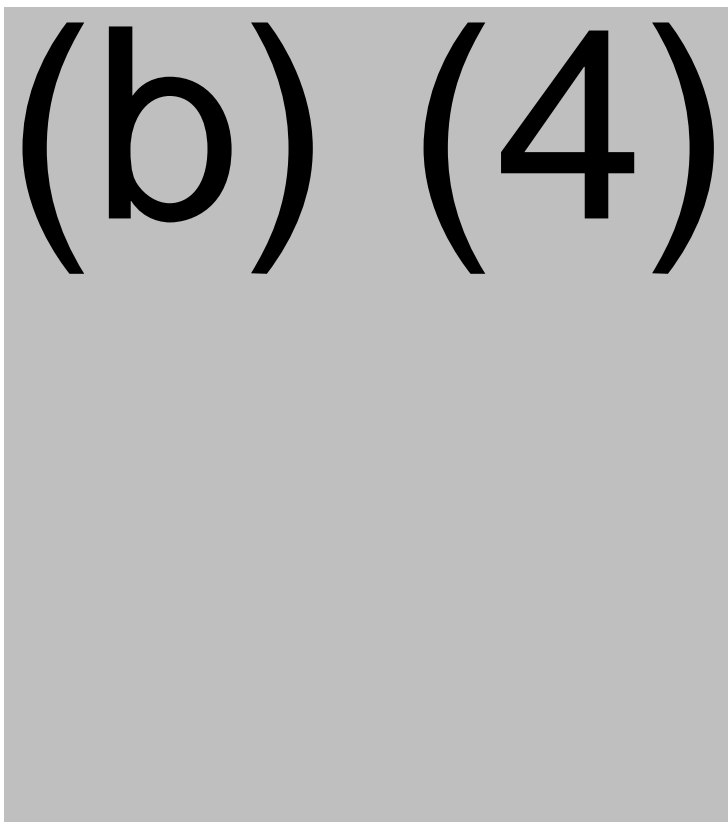
In the IR sent to the Applicant on April 4, 2022, we also asked whether the (b) (4) (b) (4) contains any color additive(s), and if so, we asked the Applicant to provide all pertinent information. The Applicant replied (April 29, 2022) stating that all bags are made using (b) (4) Class (b) (4) FEP (b) (4) and (b) (4) does not use (b) (4) are used in any components for the (b) (4)

Please see below for a description of the secondary (overwrap) and tertiary (cassette) packaging of the container closure system.

The secondary packaging, illustrated in the figure below (Figure 2; 3.2.P.7 Container Closure System), is a transparent (b) (4) thick FEP (b) (4) overwrap bag is also manufactured by (b) (4). After placing the filled (b) (4) bag in the overwrap bag, it is (b) (4) to close.

(b) (4)

The tertiary packaging is a metal cassette, illustrated in the figure below, provides physical protection for the cell product in the overwrap during storage, shipping and thawing (Figure 3; 3.2.P.7 Container Closure System).



Please see below information regarding the differences and similarities between the (b) (4) (subject of this review, cryopreservation bag) and the (b) (4) bag (manufacturing bag).

The following information from the document titled 'technical-dossier-rev-c.pdf' (starting on page 10 of 39) is provided below for the purpose of describing the differences between the (b) (4) bags and the (b) (4) bags. Of note this information related to the (b) (4) was provided by the manufacturer (b) (4),

- (b) (4) FEP bags are intended to be used for the processing of cells (e.g., sorting, transfer, culture, expansion, modification) stemming from tissues, blood, blood components and cord blood, as part of cell therapy products development and manufacturing stages.
- (b) (4) FEP bags are intended to be used for the storage, preservation (including

cryopreservation) and transportation of cell therapy medicinal products.

The manufacturer described that (b) (4) and (b) (4) FEP bags are made using (b) (4) Class (b) (4) fluorinated ethylene propylene (FEP) (b) (4) and have high oxygen permeability and low water vapor permeability coupled with a broad continuous service temperature range. According to the manufacturer FEP is an ideal material choice for a wide array of applications in cell culture and cryopreservation. The FEP (b) (4) and ports used in the bags are certified to be free of animal-derived components. The Manufacturer also described the manufacturing process for (b) (4) in the diagram below (page 11-12 of 39 of the technical-dossier-rev-c.pdf, Image 3 includes the 'Process Flow Diagram',).

(b) (4)

(b) (4)

(b) (4)

(b) (4)

III. Facility Description

In document 'technical-dossier-rev-c.pdf' (starting on page 4 of 39), it is described that the (b) (4) and (b) (4) FEP bags are manufactured in an ISO (b) (4) certified cleanroom manufacturing space located at (b) (4). The table below is an overview of the manufacturing space and core capabilities.

(b) (4)

(b) (4)

(b) (4)

IV. Drug Product Description

Elivaldogene autotemcel (eli-cel)

The drug product, eli-cel, also known as Lenti-D Drug Product, consists of an autologous CD34+ cell-enriched population containing cells transduced with lentiviral vector that encodes an ATP-binding cassette subfamily D member 1 (ABCD1) cDNA for human adrenoleukodystrophy protein (ALDP), suspended in (b) (4) cryopreservation solution containing 5% dimethyl sulfoxide (DMSO). Eli-cel is supplied as a suspension for intravenous infusion in (b) (4) 20 mL Fluoro-Ethylene-Propylene (FEP) bags.

Indications for use: Treatment of patients with Cerebral Adrenoleukodystrophy (CALD). Intended use population age: 17 years old and younger, including patients as young as 2-3 years old. The youngest patient enrolled in the clinical studies was 4 years.

Dosage: Eli-cel is administered as a single dose by intravenous infusion. Up to two (2) (b) (4) filled cyobags (total of 40 mL) may constitute a single dose. A single dose may comprise multiple drug product lots*. The number of cells per batch is (b) (4) $\times 10^6 - 30 \times 10^6$ cells/mL.

Infusion duration: The duration of the infusion does not exceed 60 minutes for each bag. Patients will only receive one single dose in their lifetime.

Shelf Life: 9 months at -140°C

The components of eli-cel are shown in the Table below (Table 1 in 3.2.P.1 Description and Composition of the Drug Product, BLA125755).

Table 1: Components of eli-cel

Component	Function	Quality Standard	Amount per Batch
Autologous CD34+ cell-enriched population containing cells transduced with lentiviral vector that encodes an <i>ABCD1</i> cDNA for human ALDP (eli-cel drug substance)	Drug substance	Specified in 3.2.P.5.1 Drug Product Specification	(b) (4) $\times 10^6$ to 30×10^6 cells/mL
(b) (4)	Excipient for suspension and preservation of cells in ultralow temperature environments	Specified in 3.2.P.4.1 Excipient Specification	20 mL per bag, up to 2 bags

ABCD1 = ATP-binding cassette subfamily D member 1; ALDP = human adrenoleukodystrophy protein.

* In this application, the terms "batch" and "lot" are used as equivalent and are used interchangeably by the Applicant.

The (b) (4) (for both drug products) is manufactured by (b) (4). The qualitative composition is provided in the table below (Table 1, 'Qualitative Composition of (b) (4) page 1 of 3.2.P.4.1 Specifications). Quality Agreements are in place to ensure Bluebird Bio will be notified of any manufacturing changes. Of note, the (b) (4) used in manufacturing has a requirement for (b) (4) of (b) (4)

1 page has been determined to be not releasable: (b)(4)

V. Reprocessing, Sterility and Shelf-Life

STERILIZATION

The information pertinent to sterilization was reviewed by the Division of Manufacturing and Product Quality (Wei Wang, CBER/OCBQ/DMPQ/MRB3). Please refer to the DMPQ memo for details on this review.

SHELF LIFE, STERILITY AND PACKAGING/SHIPPING

The Applicant proposed a (b) (4) shelf life for the (b) (4). To support the (b) (4) shelf life claim, the Applicant provided the information (obtained from the manufacturer) included in the document titled “(b) (4) -memo.pdf”. In this document (page 6 of 121), the Applicant stated that, as part of the integrity testing, they provided (b) (4) leak (b) (4), seal (b) (4) instead of product sterility testing post accelerated aging. The manufacturer added that the testing listed above together with the packaging validation and the initial sterilization validation and ongoing monitoring support (b) (4) products’ sterile shelf life (b) (4). The manufacturer also stated that this approach reflects the FDA recommendations included in the guidance titled ‘Container and Closure System Integrity Testing In lieu of Sterility Testing as a component of the stability protocol for sterile products, (February 2008).

Specifically, the (b) (4) -memo.pdf, included protocol and report VAL19-013 (attachments 2 and 3, starting on page 20 of 121). In this testing, the manufacturer studied (b) (4) cryobags to support the shelf life claim for the (b) (4). Specifically, on page 23 of 121, the manufacturer described that VAL19-013 has the following three (3) objectives.

(b) (4)



Please note that only objectives i and ii apply to the (b) (4) as the (b) (4) used in these objectives is similar to the (b) (4) whereas the (b) (4) bag included in objective iii differs in composition from the (b) (4). Please also see the clarifications, regarding the bags, provided by the Applicant below.

Upon our request for clarification (June 17, 2022), the Applicant specified (June 22, 2022) the composition of the bags tested in VAL19-013 as follows:

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(b) (4)

[REDACTED]

VAL19-013 Report

In this report the manufacturer stated that only the results related to the Shipping testing utilizing Part (b) (4) are available. The stability objective of the testing is currently undergoing real time aging.

Results

The manufacturer reports that based on the results of the data presented within this report it can be concluded that the current shipping materials and configurations are considered validated for single parcel shipping of (b) (4) FEP Bags.

Deviations

The manufacturer reported that deviation DEV-001 as follows: (b) (4)

[REDACTED]

The conclusion of the investigation was to continue with the configuration of (b) (4) bags as it still represents worst case for maximum fill and weight of the largest shipper.

INSTALLATION QUALIFICATION, OPERATIONAL QUALIFICATION, AND PERFORMANCE QUALIFICATION (IQ/OQ/PQ)

In the (b) (4) -memo.pdf, the manufacturer included attachment 1, RD2021-0020 (starting on page 5 of 121) that illustrated the installation qualification, operational qualification, and performance qualification (IQ/OQ/PQ) activities conducted on the products that they manufacture in their facility. Please see the summary of these activities below.

(b) (4)

[REDACTED]

7 pages have been determined to be not releasable: (b)(4)

(b) (4)

Reviewer comment: The results from the IQ/OQ/PQ are acceptable as they relate to the validation of the testing performed on all the bags manufactured by (b) (4). For detailed comments on the shelf life testing of the (b) (4), please refer to the reviewer recommendation box below in this section. In summary, the shipping/packaging data are adequate to support a shelf life of (b) (4) prior to use with DP and not (b) (4) as proposed by the Applicant. The Applicant agreed with this determination on June 30, 2022.

ENDOTOXIN TESTING OF THE (b) (4)

In the (b) (4) -memo.pdf (attachments 11 and 12), the manufacturer provided the Certificates of Analysis (COA) for (b) (4) lots that include the endotoxin levels. In response to our information requests (IR) from April 4 and May 13, 2022, the Applicant confirmed that the bacterial endotoxin testing was performed using the methods of (b) (4). In their response from May 20, 2022, the Applicant also provided the total estimated endotoxin levels in (b) (4) accounting for the endotoxin value of the DP (b) (4), the (b) (4); up to two bags, (b) (4) total) and the lowest weight relevant for the patient population proposed for this BLA (4-year-old patient -weight (b) (4). The levels provided were (b) (4) which is below the (b) (4) limit of (b) (4). This information is acceptable. Please see below for the COAs provided by the manufacturer.

1 page has been determined to be not releasable: (b)(4)

(b) (4)

Reviewer Recommendation

In summary, VAL19-013 includes the shipping validation and (b) (4) stability studies conducted utilizing (b) (4). The (b) (4) FEP (b) (4) bags have the same material composition of the (b) (4) with FEP (b) (4) and an IV spike port and a (b) (4) connection port that match those used in the (b) (4).

The summary report for VAL019-013, includes results from the packaging/shipping simulation testing only. This testing included (b) (4) FEP bags (representative of the (b) (4) packaged using (b) (4) packaged from (b) (4) bags per box. The following testing was performed: (b) (4)

(b) (4); visual product inspection and label legibility. The manufacturer reported that during packaging for the shipping simulation, it was observed that only (b) (4) bags of part (b) (4) were able to fit into the large shipper (b) (4) and the total weight was in-fact (b) (4). This was not in alignment with the validation where it required (b) (4) bags of part (b) (4) in the maximum configuration. However, the conclusion of the internal investigation was to continue with the configuration of (b) (4) bags as it still represents worst-case for maximum fill and weight of the largest shipper. The results from the testing listed were reported as meeting the acceptance criteria. This testing, justification for the shipper configuration used, and the results for shipping testing are acceptable.

Upon our request for clarifications (June 17, 2022), the Applicant stated (June 22, 2022) that (to date) no other report related to shelf-life testing was available. However, in the same response, the Applicant provided an update on the real time stability testing. Specifically, the Applicant stated that (b) (4) timepoint results of the stability testing have been generated and meet acceptance criteria. The Applicant also stated that the summary report for the (b) (4) timepoint is in draft and is expected to be completed by 30 July 2022 and that the (b) (4) timepoint testing is currently targeted for completion by the end of Q2 2023.

In addition, they provided the (b) (4) -memo.pdf. This memo is a certificate (dated June 21, 2022) issued by the manufacturer, where (b) (4) stated that to support the (b) (4) shelf life, a complaint review from 2013 to present was conducted and does not show a link between the product shelf-life and any complaints for functionality or issues with product sterility. In addition, on this certificate, the manufacturer stated that (b) (4) standard (unspecified product) sterilized FEP bags that were beyond their expiration date (i.e., older than (b) (4)) were evaluated for the following:

(b) (4)

The result from this testing showed that all (b) (4) bags evaluated passed a (b) (4) with no signs of damage to the product or packaging. All (b) (4) bags passed the standard (b) (4). The (b) (4) was above (b) (4) for all standard bags tested that have tubing assemblies. The manufacturer stated that, based on laboratory books studies, this (b) (4) value is comparable to other (b) (4) testing that has been completed on (b) (4) assemblies and (b) (4) assemblies. All (b) (4) values of the (b) (4) bags manufactured with standard (b) (4) was above (b) (4), with the maximum being (b) (4) the average being (b) (4) and the standard deviation being (b) (4). The historical acceptance criteria for (b) (4) of (b) (4) bags were illustrated as being (b) (4), which all expired bags met.

The manufacturer concluded that the review of historical data of product quality and the testing performed on product beyond its shelf life support no anomalies or reason for concern for product used within the certified (b) (4) shelf-life.

In their response from June 22, 2022, the Applicant also included a statement by the manufacturer (b) (4) proposing that, while the results from the completion of VAL019-013 (i.e., (b) (4) time point of the real time stability testing) are pending, they leverage the stability validation protocol performed at sister site (b) (4) for PQ10-0004 (page 13 of 121 of the of the (b) (4) -memo.pdf -Section 5.2 'Stability Validation/

Accelerated Aging-RD 2021-0020). However, PQ10-0004 included a (b) (4) accelerated and real time stability study for (b) (4) bags obtained from the suppliers (b) (4). Therefore, it is unclear what is the material composition of these bags since they are manufactured by other suppliers (i.e., (b) (4) and how the

testing conducted to those smaller (potentially different in composition) bags applies to the (b) (4) .

The Applicant also provided Table 1 (please see below) with the storage time of (b) (4) bags per lot of cell product Healthy Donor Drug Product. Based on this information, the maximum storage time of the bag before use (i.e., before filling it with drug product) was (b) (4) .

(b) (4)

In our IR from June 29, 2022, we communicated to the Applicant that, as a whole, the shelf life data provided so far (illustrated above) only supports a shelf life of (b) (4) months (b) (4) months prior filling with DP + (b) (4) months with DP). In their response from June 30, 2022, the Applicant agreed to revise the shelf life of the (b) (4) to (b) (4) DP), until additional data becomes available to support extending the shelf-life.

In summary: The Shipping/packaging data are acceptable. The Shelf-Life information was found adequate to support a shelf life of (b) (4) DP and not (b) (4) as proposed by the Applicant.

Additional Information

We sent a request to the Applicant to provide packaging testing on April 6, 2022. We requested that the Applicant ensure that the number of samples for package Performance and package Stability testing should be large enough to provide for statistically significant analysis with a high degree of reliability; for example, 95% confidence at 95% reliability or greater. Accordingly, we recommended a minimum sample size of (b) (4) for “attribute data” generated from performance tests such as (b) (4) , and a minimum sample size of (b) (4) is recommended for “variable data” generated from stability tests such as (b) (4) . On April 29, 2022, the Applicant replied that the strategy for the statistical rationale used was to test the bags to the worst-case conditions to ensure the protection of the drug product and to maintain a sterile barrier. Using (b) (4) sampling standard (b) (4) and a batch size of (b) (4) , the sample size would be (b) (4) for each of the required tests in this study with the exception of the following:

- Sterility testing per (b) (4) which requires an additional (b) (4) bags for method recovery studies, and
- (b) (4)

The Applicant also provided summary flowchart documenting the package performance and package Stability validation activities in document packaging-performance-stability-validation-summary.pdf. Please see the summary below. This information was found acceptable.

(b) (4)

1 page has been determined to be not releasable: (b)(4)

VI. Biocompatibility

Biocompatibility Information

Red = Inadequate or Unanswered

Yellow = Focal Point

There is/are 1 tissue contacting products/components/materials.

Material compositions described?: Yes

Device has Special Considerations?: No

Table of Materials and Rationales

Component	Material	Type of Contact	Identical Material & Rationale
Clear FEP (b) (4) mL bag with (b) (4)	fluorinated ethylene propylene (FEP)	Indirect	No, No Rationale

Rationale

Rationale: No rationale provided.

Biocompatibility Material 1:

Test Component/Material: Clear FEP (b) (4) mL bag with (b) (4) / fluorinated ethylene propylene (FEP)

Potential for Repeat Exposure?: No

Type of Tissue Contact: External Communicating Device: Circulating Blood

Duration of Contact: (b) (4)

Cytotoxicity Testing

Red = Inadequate or Unanswered

Yellow =

Focal Point

Cytotoxicity testing conducted: (b) (4) Method (b) (4)

Test Article: Clear FEP bag (b) (4) mL with (b) (4)

(b) (4) Conditions	Methods	Results	Conclusion and Recommendation
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(b) (4)

Cytotoxic Potential: (b) (4)

Recommendation:
Acceptable

Biocompatibility Information		Red = Inadequate or Unanswered	
Yellow = Focal Point			
(b) (4)			
Comments: Report Number V0014_130. This testing is acceptable			
Sensitization Testing		Red = Inadequate or Unanswered Yellow = Focal Point	
Sensitization testing conducted: THIS QUESTION WAS NOT ANSWERED			
Comments:			
Irritation Testing		Red = Inadequate or Unanswered Yellow = Focal Point	
Irritation testing conducted: THIS QUESTION WAS NOT ANSWERED			
Comments:			
Acute Systemic Toxicity Testing		Red = Inadequate or Unanswered Yellow = Focal Point	
Acute Systemic Toxicity testing conducted: THIS QUESTION WAS NOT ANSWERED			
Material Mediated Pyrogenicity testing conducted: THIS QUESTION WAS NOT ANSWERED			
Comments:			
Genotoxicity Testing		Red = Inadequate or Unanswered Yellow = Focal Point	
Genotoxicity testing conducted: THIS QUESTION WAS NOT ANSWERED			
Comments:			
Hemocompatibility Testing		Red = Inadequate or Unanswered Yellow = Focal Point	
Hemolysis testing conducted: THIS QUESTION WAS NOT ANSWERED			
Complement Activation testing conducted: THIS QUESTION WAS NOT ANSWERED			
Thrombogenicity testing conducted: THIS QUESTION WAS NOT ANSWERED			
Comments:			

For the purpose of biocompatibility testing, the Applicant characterized the (b) (4) as having “blood path, indirect” patient contact of limited duration (b) (4). In their original submission (document 3.2.P.2.4 Container Closure System), the Applicant included limited information related to biocompatibility, physiochemical and extractables testing received from the manufacturer (b) (4). Specifically, the Applicant provided Table 1 (document 3.2.P.2.4 Container Closure System), ‘Biocompatibility, Physiochemical, and Extractables Testing’, page 2 of 5, that summarized the testing performed. (Please see the table below). However, only

protocol # VAL-VEN-PRCL-0069 ('Extractables Simulation Study for Final Drug Product in Contact with (b) (4) Cryopreservation Bag and (b) (4) in Contact with (b) (4) Bag') and related full report #VAL-VEN-RPT-0127 were provided. This protocol and the related report included extractables testing and analysis, and the toxicological risk assessment of the extractables only.

(b) (4)

In their response to our information request, dated April 6, 2022, the Applicant provided (April 19, 2022), the reports related to biocompatibility testing (from the manufacturer (b) (4) Attachments 4-8 of the document titled (b) (4) -memo' included biocompatibility information. The biocompatibility testing was outsourced to (b) (4)

In the response from April 29, 2022, the Applicant also included document 'validation-guide-summary.pdf'. The testing included in this document was performed either with (b) (4) bags or fluorinated ethylene propylene (FEP) (b) (4) and bags. For more details, please refer to the paragraphs below.

Biocompatibility

The Applicant provided in vitro Cytotoxicity testing performed according to (b) (4) . This testing was performed using the (b) (4) mL FEP bag with (b) (4) . This bag is larger than the (b) (4) (the cryobag proposed in this submission). This testing and the results are acceptable. The results are illustrated in Appendix 1 provided below (from page 104 of 121 of the (b) (4) -memo.pdf).

(b) (4)

Reviewer Comment: The cytotoxicity testing and results are acceptable.

The Applicant also provided biocompatibility testing conducted by the manufacturer based on the (b) (4) Class (b) (4) requirements.

(b) (4) of the (b) (4) mL FEP bag with (b) (4) was used for this testing as well.

Specifically, the following (b) (4) testing was provided:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The requirements for acceptable results were set as follows:

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)


(b) (4)

This testing was reported as successful.

Reviewer Comment: This testing and the results are acceptable.

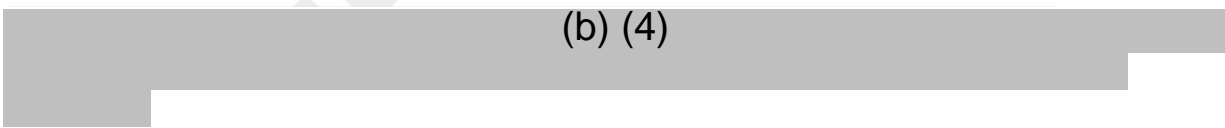
4. Pyrogen Study with Retest based on (b) (4)

This testing (found in validation-guide-summary.pdf, page 9) was carried out by (b) (4) and used sterile (b) (4) FEP bags. (b) (4) were tested. These units remained (b) (4)



(b) (4)

(b) (4)



Reviewer Comment: This testing is valid. However, because the bag tested was a (b) (4) bag and not a (b) (4) bag, these results are more relevant for the biocompatibility assessment of the manufacturing bag. However, regardless of the bag used, this is additional testing provided by the manufacturer and because we concluded that the testing per (b) (4) is adequate to

demonstrate the biocompatibility of the (b) (4) for the purpose of this BLA, there are no additional concerns about this testing and the bag used.

5. Chemical Characterization and Toxicological Risk Assessment

CDRH consults requests were sent on April 6, 2022. Felix (Zhaobo) Fan was assigned to review the extractable and leachable (E-L) information, and Caroline Pinto was assigned to review the toxicological risk assessment of the E-L.

Summaries and conclusions from the consultants' reviews are provided below.

a. Review Summary and Conclusions from Chemical Characterization Consultant Felix (Zhaobo) Fan

The Consultant, Felix Fan, reviewed information provided in the original submission (3.2.P.7 Container Closure System.pdf; 3.2.P.2.4 - Container Closure System; Full Report E-VAL-VEN-RPT-0127.pdf; Protocol # VAL-VEN-PRCL-00691) and information provided by the Applicant, upon the Consultant's request, on May 20, 2022, (Reports numbers# pi-3020, pi-3163, vrtm-119, vrtm-407, vrtm-1008, vrtm-1101).

The deficiencies identified in the extractables analysis include the following:

- i. inappropriate extraction procedure
- ii. unjustified sample processing steps
- iii. unjustified uncertainty factor value in the Analytical Evaluation Threshold (AET) determination
- iv. missing information of limits of detection (LOD) and limits of quantitation (LOQ) identification process

The Applicant also failed to provide real-time leachable study to support intended storage and use conditions throughout the proposed shelf-life.

These deficiencies were communicated to the Applicant on June 10, 2022, requesting their response by July 15, 2022.

The Consultant reviewed the Applicant's response provided on July 14, 2022.

- i. The Applicant response to the deficiency related to the inappropriate temperature used in the extraction procedure was found acceptable. Specifically, the Applicant provided the physical properties of the fluorinated ethylene propylene (the raw material of the (b) (4) and the rationale for selecting (b) (4) to simulate the storage temperature as opposed to the actual storage temperature. The Applicant stated that because the (b) (4) the temperatures chosen are appropriate. The Consultant found this acceptable.
- ii. The Applicant provided the sensitivity (b) (4) and estimated LOQ (at (b) (4)) for (b) (4) internal standards and concluded that "response of the internal standards within the samples demonstrated sufficient recovery/sensitivity after sample (b) (4) as indicated by their (b) (4) responses". However, the direct evidence to support the (b) (4) recovery rate of (b) (4) after (b) (4) step was not provided. The consultant has the

following concerns that need to be addressed before will be able to evaluate the justification of the sample processing (e.g., (b) (4) :

- a) The Applicant stated that “The primary focus of the (b) (4) analysis was (b) (4) compounds” (Page 16/ 35, 6302022_quality-info-amend). However, the (b) (4) compounds will also be captured in the (b) (4) and be detected by (b) (4) . The (b) (4) standards selected are all categorized as (b) (4) compounds with (b) (4) . Solely relying on these (b) (4) standards, which are not representative, may not lead to an accurate result in recovery rate specifically for (b) (4) compounds. The Consultant, therefore, recommends including additional (b) (4) compounds as surrogate followed with spike and recovery study. When choosing the surrogates, the Applicant should also consider widen the range of the (b) (4) so then the measured recovery rate will be still reliable when the (b) (4) of extractables are out of the range (b) (4) .
- b) The actual percentage of recovered surrogate spiked in extract should be measured to ensure most of chemicals of interest have been recovered. The acceptable recovery rate ranges from (b) (4)
- iii. The Consultant determined that, because no extractables were observed above the recommended Analytical Evaluation Threshold (AET) determination in the (b) (4) the AET deficiency has been addressed.
- iv. The Applicant only partially addressed the question related to identification of the limits of detection (LOD) and the limits of quantitation (LOQ) identification process in that they provided the methods, the system suitability, and LOQ information for each analytical technique. However, the Applicant did not provide the information requested on the identification process that was used. Therefore, the Consultant was unable to evaluate the chemical risk of the test article extract.

In addition, the Consultant recommended that the Applicant perform a leachable study, covering the full length of the shelf life proposed for the DP (i.e., 9months), using (b) (4) simulation solution and correlate the results of this study to those of the extractables study and provide the data for our review.

The deficiencies illustrated above related to the leachables study and the extractables study has been proposed as post-marketing requirement (PMR). The CBER Safety Working Committee was briefed on the PMR issues on July 14, 2022, and agreed with the CMC team’s recommendation. Information regarding the PMR request was communicated to the applicant on July 18, 2022. In addition, protocol recommendations related to the leachables and the extractables studies were sent to the Applicant on July 29, 2022. The Applicant generally agreed on the recommendations on August 4, 2022 (amendment 94) but made a few changes that the review team and the consultant did not agree upon. Therefore, the Applicant was notified on August 9, 2022, and agreed with the recommendations illustrated below August 19, 2022 (amendment 96). The Applicant provided draft protocols by August 31, 2022 for FDA’s review.

Leachable study

bluebird bio will conduct a leachable study using a simulation solution which will be maximally mimicking the properties of the DP final formulation using (b) (4) cryopreservation solution supplemented to (b) (4). This study will be conducted to cover the full length of DP proposed storage (i.e., 9 months) at the proposed storage temperature (i.e., -140°C), and reflect the use conditions, such as thawing temperature (i.e., (b) (4) at 37°C) followed by an (b) (4) room temperature hold.

Extractable study

To complement the data from the original extractable study that was provided with the BLA, bluebird bio will provide the following:

- a. To support the sample processing steps in the (b) (4) (b) (4) used in the original extractables study, we will include the following additional testing and information:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

- b. To support the compound identification process used in the extractables study, bluebird bio will provide information on the (b) (4) reference library, description of the identification process, and supporting identification information will be included in the final study report of the extractable study as requested by FDA.

Toxicological risk assessment (TRA)

Following completion of the extractable and leachable studies described above, a toxicological risk assessment will be performed to assess compounds that exceed the Analytical Evaluation Threshold (AET) following methodology described in (b) (4). The risk assessment will include a target chemical analysis of (b) (4) and assess the detected levels, even if below AET.

bluebird bio acknowledged and agreed with the (b) (4) PMR milestones and timelines language provided for BLA 125755 (Amendment 96, August 19, 2022):

1. A study to support the extractable data provided for the (b) (4) bag, including the sample processing steps in the (b) (4) and an appropriate identification process used for the extractables.

Draft Protocol Submission: August 31, 2022

Final Protocol Submission: November 30, 2022

Study Completion: February 28, 2023

Final Study Report Submission: April 30, 2023

2. A study to evaluate leachables of the (b) (4) bag over the duration of the shelf life of elivaldogene autotemcel. This evaluation will also include a full toxicological risk assessment for the identified leachables and extractables.

Draft Protocol Submission: August 31, 2022

Final Protocol Submission: November 30, 2022

Study Completion: January 30, 2024

Final Study Report Submission: March 30, 2024

For more details on the chemical characterization review, please refer to the memos provided by the Consultant (ChemicalCharacterizationConsult-ICCR00839544-BLA125717-ZhaoboFan.pdf and ChemicalCharacterizationConsult-ICCR00856661-BLA125717-ZhaoboFan.pdf) attached to this review.

b. Review Summary and Conclusions from Toxicological Risk Assessment (TRA)
Consultant Caroline Pinto

The Consultant, Caroline Pinto, reviewed information provided in the original submission (3.2.P.7 Container Closure System.pdf; 3.2.P.2.4 - Container Closure System; Full Report E-VAL-VEN-RPT-0127.pdf; Protocol # VAL-VEN-PRCL-00691), and provided the review on May 9, 2022.

The outstanding deficiency identified in this review related to the (b) (4)

(b) (4) that the Manufacturer reported in the extract of the (b) (4) bag.

In summary, (b) (4) compounds are chemicals of concern due to their bioaccumulation potential and persistence in the environment. Current scientific data indicates that exposure to high levels of certain (b) (4) compounds may lead to adverse health outcomes (e.g., reproductive/developmental toxicity, increased risk of some cancers, endocrine disruption). Because (b) (4) belongs to a chemical class of concern and the drug product is intended for young patients, the Consultant request that the Applicant conduct a toxicological risk assessment based on the quantity reported in the (b) (4) bag (b) (4) extract is recommended. The related IR for the Applicant was sent on May 13, 2022. The Applicant agreed to provide the risk assessment by July 15, 2022.

The Consultant reviewed the response provided by the Applicant on June 30, 2022. In summary, the methodology used for toxicological risk assessment of the extractable (b) (4)

(b) (4) " is in accordance with (b) (4). Specifically, the testing was conducted selecting a point of departure (POD) from a (b) (4) study for (b) (4). The No Observed Adverse Effect Level (NOAEL) of (b) (4) /day used to derive the tolerable intake (TI) value is based on a (b) (4) study for (b) (4). The consultant determined that this NOAEL is likely protective for the context of use of the (b) (4) bag (i.e., device is intended to be used for a limited contact duration of (b) (4) and repeated use does not apply). Therefore, the selected NOAEL from a repeated dose toxicity study is protective to address the acute systemic toxicity endpoint applicable for the device. The default modifying factor applied was (b) (4) for database limitations) to extrapolate the NOAEL to the TI. The calculated tolerable exposure (TE) value was (b) (4) based on (b) (4) weight patients, which corresponds to the lowest body weight of children enrolled in the clinical trials for the cell product. The dose estimate of (b) (4) used for the toxicological risk assessment is (b) (4) which corresponds to the total quantity of extractable released from (b) (4) bags. The calculated margin of safety (MoS) is (b) (4) (i.e., MoS is higher than (b) (4)). The Consultant concluded that the toxicological risk for (b) (4) is acceptable provided that the total quantity of the extractable is not underestimated.

The Consultant is concerned that the quantity and profile of (b) (4) released from the (b) (4) bags could be underestimated. To address this concern, FDA recommends conducting targeted chemical analyses of (b) (4), as well as other (b) (4) that could be present in the (b) (4) bag. She recommended that targeted chemical analyses of (b) (4) and other (b) (4) (e.g., (b) (4)) that could be present in the (b) (4) bag, to be performed to obtain an accurate exposure dose of (b) (4) for toxicological risk assessment.

She noted the following: The chemical (b) (4) belongs to the (b) (4) class of chemicals. Current scientific data indicates that exposure to certain (b) (4) may lead to liver and kidney toxicity, immune toxicity, reproductive/developmental toxicity, endocrine disruption, and increased risk for some cancers. Most of the available studies on (b) (4) toxicity have been conducted for (b) (4). Limited toxicity data is available for (b) (4), the (b) (4) reported in the extracts of the (b) (4) bag. Therefore, (b) (4) " may elicit harms that have been reported for other substances in the (b) (4) chemical class.

The request for targeted analyses of the of (b) (4), as well as other (b) (4) (e.g., (b) (4)) that could be present in the (b) (4) bag has been proposed as PMR. The CBER Safety Working Committee was briefed on the PMR issues on July 14, 2022, and agreed with the CMC team's recommendation. Information regarding the PMR study was communicated to the applicant on July 18, 2022. In addition, protocol recommendations related to the TRA were sent to the Applicant on July 29, 2022. The Applicant agreed on the recommendations on August 19, 2022 (amendment 96).

For more details regarding the TRA review, please refer to the TRA memos (TRA_ (b) (4)_BLA125717 & BLA125755.pdf; ICC2200597_BLA125717_TRA_ (b) (4).pdf) attached to this review.

(b) (4)

Reviewer Recommendation

The Biocompatibility information is acceptable.

For the purpose of biocompatibility testing, the Applicant characterized the (b) (4) as having "blood path, indirect" patient contact of limited duration (b) (4)

According to the FDA guidance titled 'Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"', the following testing should be provided for device that have blood path indirect contact for (b) (4): cytotoxicity, sensitization, irritation

or intracutaneous reactivity, acute systemic toxicity, and hemocompatibility, and the FDA recommended material-mediated pyrogenicity.

However, the Applicant only provided cytotoxicity testing per (b) (4). The cytotoxicity testing and the results are acceptable. No additional testing per (b) (4) was requested because the Applicant provided biological reactivity testing based on (b) (4). However, a risk assessment for waiving sensitization and hemocompatibility testing was requested and the Applicant agreed to provide this by June 30, 2002.

The Applicant provided the risk assessment on June 30, 2022 (ven-rpt-0893.pdf). In this risk assessment the Applicant referred to the TRA assessment related to the (b) (4)

that our CDRH consultant, Caroline Pinto, found deficient and for which we asked a post-marketing requirement. Specifically, the consultant is concerned that the quantity and profile of (b) (4) released from the (b) (4) bags could be underestimated in the Applicant assessment due to the deficiency in the extractables study (Please see the discussion related to the toxicological risk assessment provided below in this memo) and the lack of leachable study.

In summary, to justify the waiving the hemocompatibility testing, the Applicant referred to the (b) (4)-day repeat dose study in rats, where the hemotoxic effects for (b) (4) were observed only at (b) (4) /day. The Applicant stated that this dose is (b) (4) times higher than the potential patient exposure from the use of the (b) (4) as proposed in this BLA. To support the waiving of the sensitization testing, the Applicant referred to the (b) (4) test performed using (b) (4). The Applicant stated that this test was negative, and no local corrosive effects were noted, and the structurally similar compound (b) (4) was not a skin or eye irritant (b) (4).

As mentioned above, the TRA assessment that the Applicant referred in their risk assessment may be deficient, therefore it is unclear whether the risk assessment provided is acceptable. However, for the purpose of biocompatibility testing, the Applicant also provided biological reactivity testing performed according to (b) (4) (details below). This testing was found sufficient for the purpose of the biocompatibility safety of the (b) (4). Of note, the Applicant will be asked to conduct targeted chemical analyses of (b) (4) (b) (4) as well as other (b) (4) (e.g., (b) (4)) that could be present in the (b) (4) bag, as post-marketing requirement. This is necessary to ensure that (b) (4) compounds released from the (b) (4) bag are not underestimated and will present acceptable toxicological risk in accordance with the FDA 2020 Biocompatibility Guidance on the Use of ISO 10993-1.

The biological reactivity testing provided by the Applicant was performed according to (b) (4). Based on FDA guidance 'Container Closure Systems for Packaging Human Drugs and Biologics' (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/container-closure-systems-packaging-human-drugs-and-biologics>), for plastic components (such as the (b) (4)), data from (b) (4) will typically be considered sufficient evidence of safety. However, because the (b) (4) is (b) (4) and the vehicle of the cell product (b) (4) has a (b) (4) between (b) (4) and contains a solubilizing agent (e.g., DMSO), the lead reviewer questioned the appropriateness of the temperature and duration (b) (4) hours) and extraction solutions used in the extraction method implemented in the (b) (4).

(Please see table 4 below for more details on the guidance recommendations for injectable drug products). The related IR sent on June 10, 2022.

The Applicant replied (June 30, 2022) that according to (b) (4)

The Applicant justification for the appropriateness of the temperature and duration used in the extraction methods used in the biological reactivity testing is acceptable. This part of the Applicant's response was reviewed by Dr. Bao Nguyen.

In addition, the Applicant also provided a justification for the use of the extraction solution used. Specifically, the Applicant indicated that a (b) (4) solution is similar to the (b) (4) solutions. Therefore, the leaching propensity and lack of toxicity and irritation demonstrated in the (b) (4) studies using the (b) (4) solutions are representative of the extraction properties with respect to biological reactivity and reflect the (b) (4) of the 5% DMSO (b) (4) media used for formulation of the DP. To gather some additional insight on these extraction solutions and their intent in these studies, Dr. Alyssa Kitchel (device TL) reached out to Dr. Zhaobo (Felix) Fan, CDRH consultant for the E&L review. The inquiry and the Consultant's response is provided below. Overall, Dr. Kitchel agreed with Dr. Fan's insights and considers the Applicant's response to this IR acceptable. No further information is needed.

TEB Inquiry (from Dr. Alyssa Kitchel to Dr. Zhaobo (Felix) Fan):

In FDA's container closure guidance it states that for plastic container closure systems (such as the (b) (4)) that contain injectable drug products, if the extraction properties of the drug product vehicle differ reasonably from the extraction properties of water (e.g., due to (b) (4)), it is recommended that the biological reactivity testing (Biocompatibility testing) is performed using the drug product vehicle. As you know the Applicant has been utilizing a simulation solution for their (b) (4) solution for a variety of extraction protocols. It appears that (b) (4) solution has a similar (b) (4) to recommended (b) (4) solvents used in these extraction tests - (b) (4) . Additionally recommended (b) (4) solvents were used - (b) (4) as extraction solutions. These (b) (4) are recommended per (b) (4) .

I wanted to get your insights on a few questions I have:

1. For such recommended extraction solutions, is the intent to capture a range of (b) (4) by using different extraction solutions?
2. Aside from (b) (4) , would you consider (b) (4) solution to be reasonably different from the extraction properties of water per FDA's container closure guidance? Specifically, should there be concerns if the (b) (4) solution was not used as an extraction solvent to examine biocompatibility, or would the (b) (4) ranges of the recommended solutions be sufficient from an extraction perspective?

Response (Zhaobo (Felix) Fan):

I did look at the 1999 guidance for container closure systems before generating the consult memo. Here is the answer to your questions:

1. Yes, the diversity of extraction vehicle meant to capture the extractables with different (b) (4) . Usually, the compounds can be extracted at higher yield by the solvent with (b) (4) (it doesn't mean the compounds with (b) (4) will not come out). In order to analyze the worst-case scenario, at device world, we typically request Applicant extracting using (b) (4) .
2. Other than the (b) (4) , I will **NOT** define that (b) (4) solution "differ reasonably from the extraction properties of water". But, I think the original quote from the 1999 guidance was to compare the extraction properties between the **drug product** and **water**. Since the biological formulation of solution is complicated, it is hard to estimate the difference in extraction properties when comparing with water. Although Applicant used (b) (4) for the simulation study, they still provide the (b) (4) extraction according to (b) (4) . From my perspective, Applicant did not challenge whether the extraction properties are reasonably different between product and the water, rather providing the testing result. The approach seems good to me. With respect to the (b) (4) simulation study, it was performed for the different

purpose (i.e., identify the specific chemicals that of safety concern) which may not be fair to be compared with the biological reactivity testing. For device review at CDRH, the selection of extraction solvent and condition may be different between chemical characterization and biocompatibility testing.

Please table 4 below (page 26 of 56) from the above-mentioned guidance that illustrates the information that should be submitted for injectables or ophthalmic drug products.

Table 4
Information That Typically Should Be Submitted for Injectable
or Ophthalmic Drug Products

Description	<p>Overall general description of container closure system, plus:</p> <p><u>For Each Packaging Component:</u></p> <ul style="list-style-type: none"> • Name, product code, manufacturer, physical description • Materials of construction (for each: name, manufacturer and product code) • Description of any additional treatments (e.g., procedures for sterilizing and depyrogenating packaging components)
Suitability	<p><u>Protection:</u> (By each component and/or the container closure system, as appropriate)</p> <ul style="list-style-type: none"> • Light exposure, when appropriate • Reactive gases (e.g., oxygen) • Moisture permeation (powders) • Solvent loss (liquid-based dosage forms) • Sterility (container integrity) or increased bioburden • Seal integrity or leak testing of tubes (ophthalmics) <p><u>Safety:</u> (for each material of construction, as appropriate)</p> <ul style="list-style-type: none"> • Chemical composition of all plastics, elastomers, adhesives, etc.* • For elastomeric closures: USP Elastomeric Closures for Injections testing • For glass components: USP Containers: Chemical Resistance — Glass Containers • For plastic components and coatings for metal tubes: USP Biological Reactivity Tests • If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., due to high or low pH or due to a solubilizing excipient), then drug product should be used as the extracting medium. • If the total weight of extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. • For plastic or elastomeric components undergoing heat sterilization, it is current practice to request that the extraction profile be obtained at 121 °C/1 hour using an appropriate solvent. <p><u>Compatibility:</u> (for each component and/or the packaging system, as appropriate)</p> <ul style="list-style-type: none"> • For coatings on metal tubes: Coating integrity testing • For elastomeric components: Evaluation of swelling effects • For plastic components (including tube coatings): USP Containers: Physicochemical Tests - Plastics testing • For ophthalmics: Particulate matter and eye irritants • Stability studies also support compatibility <p><u>Performance:</u> (For the assembled packaging system)</p> <ul style="list-style-type: none"> • Functionality and/or drug delivery

Quality Control	<p><u>For Each Packaging System Received by the Applicant:</u></p> <ul style="list-style-type: none"> • Applicant's tests and acceptance criteria^a • Dimensional (drawing) and performance criteria • Method to monitor consistency in composition of most plastic and elastomeric components (e.g., periodic comparison to the original extraction profile is recommended) <p><u>For Each Packaging Component Provided by the Supplier:</u></p> <ul style="list-style-type: none"> • Manufacturer's acceptance criteria for release, as appropriate • Description of the manufacturing process, as appropriate (e.g., procedure/validation for sterilization and depyrogenation)
Stability	<ul style="list-style-type: none"> • See section III.C.4

^a Including any additives used in the manufacture of a packaging component

^b Testing for plastics should be performed on the packaging component, not on the unformed resin.

^c Note that applicant's acceptance tests may include, among others, test parameters indicated under the description, suitability, and quality control sections of this table.

^d Refer to the *Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug* (November 1994).

Additional Information

In our IR from June 10, 2022, the Applicant was asked to specify the differences and similarities of the bag used in the biological reactivity testing (b) (4) mL FEP bag with (b) (4)) and how the testing performed with the (b) (4) mL FEP bag is supportive of the safe use of the (b) (4) for the purpose of this BLA.

The Applicant replied that the (b) (4) mL bag has (b) (4) , while the (b) (4) only has (b) (4) (Figure 1 below). Additionally, although the (b) (4) has additional components that are part of the (b) (4) , the Applicant claims that these components are non-product contacting and are not part of the fluid path. Figure 2 (provided below) indicates that the retaining ring and sleeve components are on the outside of the (b) (4) tubing and do not contact the fluid path. To support the biocompatibility of the (b) (4) , the Applicant also attached a "biocompatibility statement" from (b) (4) , the manufacturer of (b) (4) bags. The document contains a table outlining the biocompatibility tests conducted on all the components used to manufacture the DP bag. For all of the fluid-contacting components, the bag manufacturer has provided a description of the biocompatibility studies that were conducted, with the exception for part (b) (4) (b) (4) . For these (b) (4) components, the bag manufacturer states that "This part is purchased and not manufactured by (b) (4) . Per the manufacturer, the part is (b) (4) Class (b) (4) Compliant."

In an informal teleconference call with the Applicant on July 13, 2022, the Applicant clarified that the materials used in the (b) (4) is the (b) (4) as the (b) (4) component, and that the (b) (4) mL FEP bag has a luer bag connection made from the (b) (4) . Therefore, although the luer bag connections are different between the (b) (4) bags, they are made from the (b) (4) This indicates that the biocompatibility tests conducted on the (b) (4) mL FEP bag included the materials used in the (b) (4) components and were therefore

adequately assessed. This response was reviewed by Dr. Bao Nguyen and found acceptable.

As mentioned above, the Applicant provided an acceptable justification as to why the (b) (4) mL FEP bag is representative of the (b) (4) used for DP storage. The Applicant indicated that the (b) (4) mL FEP bag is manufactured from the same materials and was studied under similar conditions (b) (4) to determine biocompatibility. In an informal teleconference held on July 13, 2022, the Applicant was asked about the extraction conditions referred to in this response compared to the extraction conditions referred to in response to IR 6 Comment 8 Question 3. In response, the Applicant provided written clarification (received July 15, 2022) stating that the extraction vehicles described in this response were used as part of a separate biocompatibility study performed for the (b) (4) mL bag (as documented in (b) (4) report PVS-R19115 submitted in Sequence 0050), included (b) (4) and are not related to the extraction conditions described for the (b) (4) performed according to (b) (4) (discussed in Question 3). Therefore, this clarification is sufficient, and the Applicant has adequately demonstrated that the (b) (4) mL FEP bag is acceptable as a representative for the (b) (4) for the purpose of the biocompatibility testing.

(b) (4)

(b) (4)

VII. [Labeling](#)

In technical-dossier-rev-c.pdf (page 14 of 39), the Applicant provided the (b) (4) labels.

The label is reviewed by the consult requestor.

(b) (4)

VIII. [Performance Testing OR Verification & Validation](#)

1. Capacity Testing

In our information request from April 4, 2022, we asked the Applicant to provide capacity testing (including fluidity, filling and emptying testing) to demonstrate that the (20 mL) volume that they propose is appropriate for the (b) (4) size that they propose in this submission.

The Applicant provided a response to this request, on April 29, 2022, stating that the capacity testing was not performed by the Manufacturer of the bag (b) (4) and that the nominal volume of the product is 20 mL and that the maximum fill volume of the (b) (4) is (b) (4). The review team discussed this information on May 9 2022, and agreed that given the maximum fill capacity is significantly larger than the DP volume, the capacity testing can be waived for the purpose of this BLA.

2. Integrity Testing (PMC)

In our information request from April 4, 2022, we asked the Applicant to provide testing to demonstrate that the (b) (4) retains its integrity after worst-case conditions (e.g., (b) (4) and any other manipulation(s) relevant to its intended use for the purpose of this BLA. On April 29, 2022, the Applicant replied referencing the shipping simulation study and real time shelf life (stability) studies performed included in VAL019-013 discussed above. The testing included in VAL019-013 is performed using the representative (b) (4) cryobags. Therefore, the testing in VAL019-013 is not sufficient to demonstrate that the (b) (4) is resilient to worst-case conditions. We requested that the Applicant provide this testing by June 30, 2022. However, in their response (June 30, 2022), the Applicant proposed to conduct (b) (4) testing following worst-case scenario conditioning, specifically including (b) (4). In our communication regarding post-marketing commitments (PMC), dated July 18, 2022, we requested the Applicant to commit to perform visual inspection testing following (b) (4)

(b) (4). We also asked that the complete test reports for this testing be submitted for our review on or before December 31, 2022. On August 17, 2022, (amendment 93), the Applicant agreed to provide this testing per our recommendations.

3. Suspension (hanger eyelet) testing

In our information request (IR) from April 4, 2022, we asked the Applicant to provide suspension (hanger eyelet testing). The Applicant replied (April 29, 2022) that this testing was not performed by the manufacturer and that the FEP (b) (4) meets the FEP (b) (4) meets (b) (4). In our follow-up IR (dated May 13, 2022), we communicated to the Applicant that the (b) (4) criterion of the (b) (4) FEP (b) (4) might not be applicable to the parts of the bags nearing the (b) (4), which may have different mechanical properties than the (b) (4). Therefore, we requested again suspension (hanger eyelet) testing of the (b) (4) to show that this container closure, especially around the (b) (4), is safe when used as intended. In their response from May 20, 2022, the Applicant proposed to provide the testing by July 15, 2022. We replied on June 10, 2022, asking that they provided the testing on June 30, 2022, to allow for sufficient review time. On June 30, 2022, the Applicant provided hanger eyelet testing conducted according to (b) (4).

Specifically, the testing was illustrated as follows:

The (b) (4) bags were filled with (b) (4) cryopreservation media (b) (4) as a surrogate to the final drug product as it is the drug product formulation solution. The bags were packaged within metal cassettes, cryopreserved, and then (b) (4)

(b) (4) . Furthermore, to account for the longest acceptable administration time, all bags were subjected to (b) (4)

(b) (4)

None of the bags fell. Photographs were taken and eyelets were compared to the control bag – some stretching was evident with time progression, but film around the eyelet is still intact and remained functionally intact throughout testing. There were no protocol deviations.

Reviewer Comment: This testing and results are acceptable. This testing was reviewed by Dr. Bao Nguyen.

4. (b) (4) Testing (PMC)

To our request to provide (b) (4) testing (April 4, 2022), the Applicant responded that (b) (4) studies performed with the cryoshipper (where the (b) (4) is contained in the overwrap and cassette) showed that the no damage to the (b) (4) (b) (4) was identified. However, this testing does not demonstrate that the (b) (4) can withstand (b) (4) when used on its own (i.e., without the overwrap and the cassette and the cryoshipper). Therefore, on July 18, 2022, we requested the Applicant, to commit to perform (b) (4) testing of the filled (b) (4) (filled to nominal capacity) as a post-marketing commitment. We suggested the Applicant could use (b) (4) as guideline, and provide justifications for the test method, results, and conclusions as part of a complete test report. We asked that the results for this (b) (4) testing on the (b) (4) bag be submitted for our review on or before December 31, 2022. On August 17, 2022, (amendment 93), the Applicant agreed to provide this testing per our recommendations.


5. Analysis of (b) (4) Testing

Upon our request for particulate testing (April 4, 2022), the Applicant provided a document titled (b) (4) -memo.pdf including validation protocol and the interim report for this testing (attachment 9, starting on page 105 of 121). The information listed below was obtained from the Manufacturer (b) (4) by the Applicant.

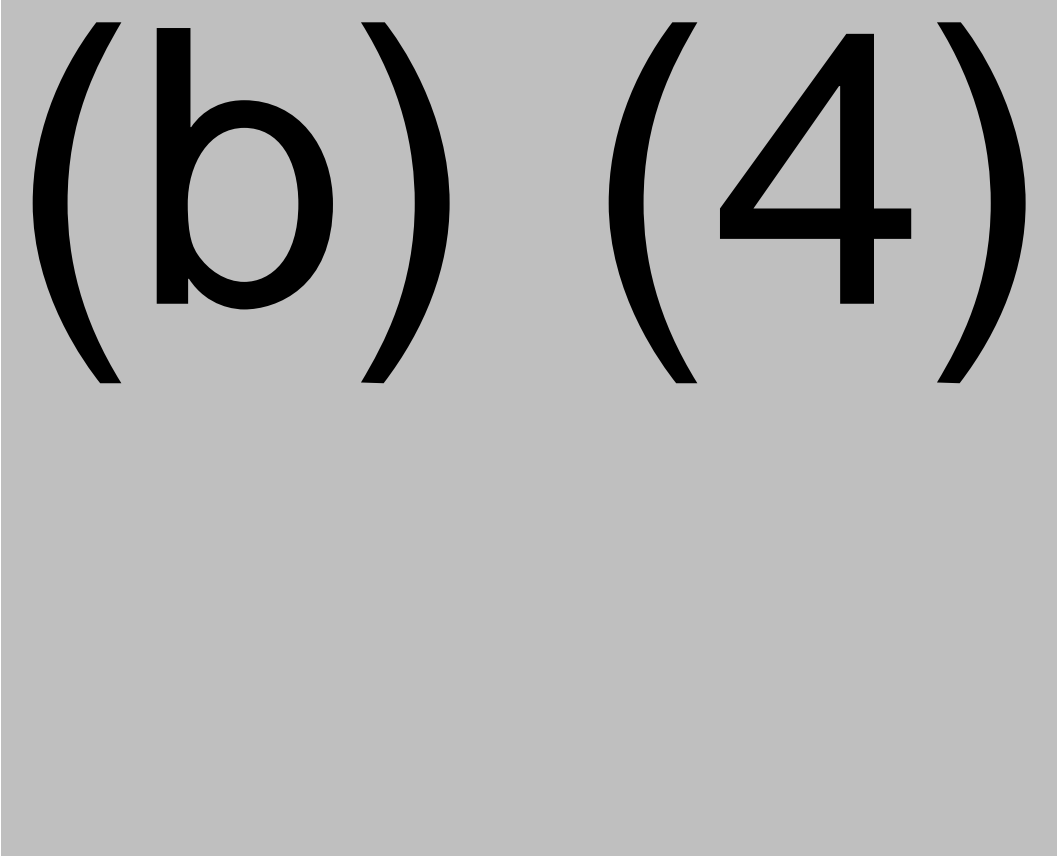
(b) (4)

1 page has been determined to be not releasable: (b)(4)

(b) (4)



(b) (4)



The manufacturer reported that all acceptance criteria were met for this batch.

Reviewer Comment: The testing planned, and the preliminary results are acceptable.

Reviewer Recommendation

The Performance Testing [Verification & Validation] is **incomplete**.
Please see reviewer comments for each testing.

I recommend that the Applicant provide (b) (4) testing, and integrity testing after
(b) (4) as part of post-marketing commitments (PMCs).

IX. Interactive Review Summary

1. On April 6, 2022, an information request related to the testing that was missing (capacity, hanger eyelet, integrity testing, (b) (4) testing, endotoxin testing, integrity after (b) (4)) and related results was sent to the Applicant. Partial information was provided on April 29, 2022.
2. On May 13, 2022, a request followed asking (again) the Applicant to provide for some of the testing listed above (e.g., hanger eyelet, integrity after (b) (4)), because the justification for not conducting the testing was not adequate. The Applicant provided a partial response on May 20, 2022.
3. The following requests were sent to BLA125717, however, the apply to BLA125755 as well. Therefore, the Applicant was asked to provide the same information as amendments to BLA125755. The Applicant submitted their response to BLA125755 (this BLA) July 15, 2022:

On June 6, 10, 29, 2022, requests for clarification related to the appropriateness of the bags tested in the shelf life and shipping/packaging testing, and the E&L and TRA assessment were sent to the Applicant. The Applicant replied. Their responses received on June 30, 2022, only partially answered the E&L and TRA questions. On June 29, 2022, the Applicant was asked to revise the shelf life and propose a shelf life that reflects the testing and results available to date. The Applicant agreed in their response dated June 30, 2022. On July 13, 2022, an additional clarification request regarding the bag(s) and components used in the biocompatibility testing was sent. The Applicant provided sufficient details on July 15, 2022.

4. In our communication regarding post-marketing commitments (PMC), dated July 18, 2022, we requested the Applicant to commit to perform visual inspection testing following (b) (4) (e.g., (b) (4)) with a maximum fill volume, using at least a (b) (4) solution, instead of performing (b) (4) testing. We specified that the testing should include, but not be limited to, visual inspection to assess for tears, cracks, and breaks after (b) (4) . We also asked that the complete test reports for this testing be submitted for our review on or before December 31, 2022. On August 17, 2022, (amendment 93), the Applicant agreed to provide this testing per our recommendations.
5. On July 18, 2022, we requested the Applicant, to commit to perform (b) (4) testing of the filled (b) (4) (filled to nominal capacity) as a PMC as well. We suggested the Applicant could use (b) (4) as guideline, and provide justifications for the test method, results, and conclusions as part of a complete test report. We asked that

the results for this (b) (4) testing on the (b) (4) bag be submitted for our review on or before December 31, 2022. On August 17, 2022, (amendment 93), the Applicant agreed to provide this testing per our recommendations.

6. Information regarding the PMR request was communicated to the applicant on July 18, 2022. In addition, protocol recommendations related to the leachables and the extractables studies were sent to the Applicant on July 29, 2022. The Applicant agreed with our recommendations August 19, 2022, and (Amendment 96).

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Carolina Panico Biologist Lead Reviewer OTAT/DCGT/TEB	Concur	
Alyssa Kitchel Team Leader OTAT/DCGT/TEB	Concur	
Bao-Ngoc Nguyen Scientific Reviewer OTAT/DCGT/TEB	Concur	
Laura Ricles Branch Chief OTAT/DCGT/TEB	Concur	

APPENDIX A. REVIEW SUMMARY PROVIDED TO GTB FOR THE PURPOSE OF ADDING THE (b) (4) REVIEW ASSESSMENTS TO THE BLA MEMO.

1. Container Closure (for the Drug Product) Description

The container closure system proposed in BLA125755 consists of a primary package container, the (b) (4) Cryopreservation bag (subject of this review), a secondary package container ((b) (4) Overwrap bag), and a tertiary package container (cryocassette).

The primary container closure, subject of this review, is a 20-mL fluorinated ethylene propylene (FEP) cryopreservation bag with maximum fill volume of (b) (4). The (b) (4) is manufactured by (b) (4)

Please see Table 1 and Figure 1 below (from 3.2.P.7 Container Closure System, page 3) for the specifications and representative drawings of the (b) (4)

Table 1: Specifications/Technical Information for (b) (4) Bag

Bag material	(b) (4)
Spike port with septum, protected with FEP cover	
Inlet tubing	
Female Luer	
Pinch clamp	
Inside bag dimensions	
Outside bag dimensions (including port and label pouch)	
Working temperature	

(b) (4)

(b) (4)

1. Shelf Life, Packaging, Shipping

For the purpose of specifically supporting the shelf life ((b) (4) at temperature (b) (4) to be confirmed), and packaging and shipping claims, the manufacturer initiated protocol VAL19-013 (attachment 2 of the (b) (4) -memo.pdf) and provided the summary report (attachment 3 of the (b) (4) -memo.pdf). VAL19-013 include objective 1 (Shipping Validation utilizing Part # (b) (4)) and 2 (A (b) (4) stability study of the worst case (b) (4) FEP bag assemblies exposed to a (b) (4) which will support rework and (b) (4) for all marketed sizes up to (b) (4) of VAL19-013. These two objectives apply to the (b) (4) . The Shipping/packaging data provided is acceptable. However, the Shelf-Life

information was found adequate to support a shelf life of (b) (4) prior to use with DP. This assessment was communicated to the Applicant on June 29, 2022. The Applicant agreed (on July 15, 2022) to revise the shelf life of the (b) (4) to (b) (4) prior to use (before filling it with DP), until additional data becomes available to support extending the shelf-life.

2. Biocompatibility

For the purpose of biocompatibility testing, the Applicant characterized the (b) (4) as having "blood path, indirect" patient contact of limited duration (b) (4) according to the FDA guidance titled 'Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"'. The following testing should be provided for devices that have blood path (b) (4) cytotoxicity, sensitization, irritation or intracutaneous reactivity, acute systemic toxicity, and hemocompatibility, and the FDA recommended material-mediated pyrogenicity. However, the Applicant only provided cytotoxicity testing per (b) (4). The cytotoxicity testing per (b) (4) and related results are acceptable. No additional testing per (b) (4) was requested because the Applicant provided biological reactivity testing based on (b) (4). However, a risk assessment for waiving sensitization and hemocompatibility testing was requested and the Applicant agreed to provide this risk assessment by June 30, 2002.

The Applicant also biological reactivity testing provided by the Applicant was performed according to (b) (4) and included (b) (4).

Based on the FDA guidance 'Container Closure Systems for Packaging Human Drugs and Biologics' (<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/container-closure-systems-packaging-human-drugs-and-biologics>), for plastic components (such as the (b) (4)), data from (b) (4) Biological Reactivity Tests would typically be considered sufficient evidence of safety. The biocompatibility information provided was found acceptable.

3. Chemical Characterization (Post Marketing Requirement)

The Consultant, Felix (Zhaobo) Fan, reviewed information provided in the original submission (3.2.P.7 Container Closure System.pdf; 3.2.P.2.4 - Container Closure System; Full Report E-VAL-VEN-RPT-0127.pdf; Protocol # VAL-VEN-PRCL-00691) and information provided by the Applicant, upon the Consultant's request, on May 20, 2022, (Reports numbers# pi-3020, pi-3163, vrtm-119, vrtm-407, vrtm-1008, vrtm-1101).

The deficiencies identified in the extractables analysis include the following:

- i. inappropriate extraction procedure
- ii. unjustified sample processing steps
- iii. unjustified uncertainty factor value in the Analytical Evaluation Threshold (AET) determination
- iv. missing information of limits of detection (LOD) and limits of quantitation (LOQ) identification process

The Applicant also failed to provide real-time leachable study to support intended storage and use conditions throughout the proposed shelf-life.

These deficiencies were communicated to the Applicant on June 10, 2022, requesting their response by July 15, 2022.

The Consultant reviewed the Applicant's response provided on July 15, 2022.

- i. The Applicant response to the deficiency related to the inappropriate (b) (4) used in the extraction procedure was found acceptable. Specifically, the Applicant provided the physical properties of the fluorinated ethylene propylene (b) (4)

(b) (4)

The Consultant found this acceptable.

- ii. The Applicant provided the sensitivity (b) (4) and estimated LOQ (at (b) (4)) for (b) (4) standards and concluded that "response of the internal standards within the samples demonstrated sufficient recovery/sensitivity after sample (b) (4) as indicated by their (b) (4) responses". However, the direct evidence to support the (b) (4) recovery rate of analytes after (b) (4) step was not provided. The consultant has the following concerns that need to be addressed before will be able to evaluate the justification of the sample processing (e.g., (b) (4))

- a) The Applicant stated that "The primary focus of the

(b) (4)

(b) (4)

- iii. The Consultant determined that, because no extractables were observed above the recommended (b) (4)

deficiency has been addressed.

- iv. The Applicant only partially addressed the question related to identification of the limits of detection (LOD) and the limits of quantitation (LOQ) identification process in that they provided the methods, the system suitability, and LOQ information for each analytical technique. However, the Applicant did not provide the information

requested on the identification process that was used. Therefore, the Consultant was unable to evaluate the chemical risk of the test article extract.

In addition, the Consultant recommended that the Applicant perform a leachable study, covering the full length of the shelf life proposed for the DP (i.e., 9 months for eli-cel), using (b) (4) simulation solution and correlate the results of this study to those of the extractables study and provide the data for our review.

The deficiencies illustrated above related to the leachables study and the extractables study has been proposed as a post-marketing requirement (PMR). The CBER Safety Working Committee was briefed on the PMR issues on July 14, 2022, and agreed with the CMC team's recommendation. Information regarding the PMR study was communicated to the applicant on July 18, 2022.

For more details on the chemical characterization review, please refer to the memos provided by the Consultant (ChemicalCharacterizationConsult-ICCR00839544-BLA125717-ZhaoboFan.pdf and ChemicalCharacterizationConsult-ICCR00856661-BLA125717-ZhaoboFan.pdf) attached to this review.

4. Toxicological Risk Assessment (TRA) (Post Marketing Requirement)

The Consultant, Caroline Pinto, reviewed information provided in the original submission (3.2.P.7 Container Closure System.pdf; 3.2.P.2.4 - Container Closure System; Full Report E-VAL-VEN-RPT-0127.pdf; Protocol # VAL-VEN-PRCL-00691), and provided the review on May 9, 2022.

The outstanding deficiency identified in this review related to the (b) (4)

(b) (4) that the Manufacturer reported in the extract of the (b) (4) bag.

In summary, (b) (4) compounds are chemicals of concern due to their bioaccumulation potential and persistence in the environment. Current scientific data indicates that exposure to high levels of certain (b) (4) compounds may lead to adverse health outcomes (e.g., reproductive/developmental toxicity, increased risk of some cancers, endocrine disruption). Because (b) (4)

(b) (4) belongs to a chemical class of concern and the drug product is intended for young patients, the Consultant request that the Applicant conduct a toxicological risk assessment based on the quantity reported in the (b) (4) bag (b) (4) extract is recommended. The related IR for the Applicant was sent on May 13, 2022. The Applicant originally replied that they would provide the risk assessment by July 15, 2022. However, upon our follow-up request, the Applicant agreed to provide the risk assessment by June 30, 2022.

The Consultant reviewed the response provided by the Applicant on June 30, 2022. In summary, the methodology used for toxicological risk assessment of the extractable (b) (4) (b) (4) is in accordance with (b) (4)

(b) (4) Specifically, the testing was conducted selecting a point of departure (POD) from a (b) (4) study for (b) (4)

. The No Observed Adverse Effect Level (NOAEL) of (b) (4) /day used

to derive the tolerable intake (TI) value is based on a (b) (4) study for (b) (4). The consultant determined that this NOAEL is likely protective for the context of use of the (b) (4) bag (i.e., device is intended to be used for a limited contact duration of (b) (4) use does not apply). Therefore, the selected NOAEL from a repeated dose toxicity study is protective to address the acute systemic toxicity endpoint applicable for the device. The default modifying factor applied was (b) (4) to extrapolate the NOAEL to the TI. The calculated tolerable exposure (TE) value was (b) (4) based on (b) (4) weight patients, which corresponds to the lowest body weight of children enrolled in the clinical trials for the cell product. The dose estimate of (b) (4) used for the toxicological risk assessment is (b) (4) which corresponds to the total quantity of extractable released from four (b) (4) bags. The calculated margin of safety (MoS) is (b) (4) (i.e., MoS is higher than (b) (4)). The Consultant concluded that the toxicological risk for (b) (4) is acceptable provided that the total quantity of the extractable is not underestimated.

The Consultant is concerned that the quantity and profile of (b) (4) released from the (b) (4) bags could be underestimated. To address this concern, FDA recommends conducting targeted chemical analyses of (b) (4), as well as other (b) (4) that could be present in the (b) (4) bag. She recommended that targeted chemical analyses of (b) (4), and other (b) (4) that could be present in the (b) (4) bag, to be performed to obtain an accurate exposure dose of (b) (4) for toxicological risk assessment.

She noted the following: The chemical (b) (4) belongs to the (b) (4) class of chemicals. Current scientific data indicates that exposure to certain (b) (4) may lead to liver and kidney toxicity, immune toxicity, reproductive/developmental toxicity, endocrine disruption, and increased risk for some cancers. Most of the available studies on (b) (4) toxicity have been conducted for (b) (4). Limited toxicity data is available for (b) (4) the (b) (4) reported in the extracts of the (b) (4) bag. Therefore, (b) (4) may elicit harms that have been reported for other substances in the (b) (4) chemical class. The request for targeted analyses of the (b) (4), as well as other (b) (4) (e.g., (b) (4)) that could be present in the (b) (4) bag has been proposed as PMR. The CBER Safety Working Committee was briefed on the PMR issues on July 14, 2022 and agreed with the CMC team's recommendation.

Information regarding the PMR study was communicated to the applicant on July 18, 2022.

For more details regarding the TRA review, please refer to the TRA memos (TRA_ (b) (4) _BLA125717 & BLA125755.pdf; ICC2200597_BLA125717_TRA_ (b) (4) .pdf) attached to this review.

5. Endotoxin Testing

In the (b) (4) -memo.pdf (attachments 11 and 12), the manufacturer provided the Certificates of Analysis (COA) for (b) (4) lots that include the endotoxin levels of the (b) (4) . In response to our information requests (IR) from April 4 and May 13, 2022, the Applicant confirmed that the bacterial endotoxin testing was performed using the methods of (b) (4) . In their response from May 20, 2022, the Applicant also provided the total estimated endotoxin levels in (b) (4) accounting for the endotoxin value of the DP (b) (4) and the (b) (4) and the lowest weight relevant for the patient population proposed for this BLA ((b) (4)-old as the youngest patient, weight (b) (4) . The levels provided were (b) (4) which is below the (b) (4) limit of (b) (4) . This is acceptable.

1. Integrity Testing (Post Marketing Commitment)

In our information request from April 4, 2022, we asked the Applicant to provide testing to demonstrate that the (b) (4) retains its integrity after worst-case conditions (e.g., (b) (4) and any other manipulation(s) relevant to its intended use for the purpose of this BLA. On April 29, 2022, the Applicant replied referencing the shipping simulation study and real time shelf life (stability) studies performed included in VAL019-013 discussed above. The testing included in VAL019-013 is performed using the representative (b) (4) cryobags. Therefore, the testing in VAL019-013 is not sufficient to demonstrate that the (b) (4) is resilient to worst-case conditions. We requested that the Applicant provide this testing by June 30, 2022. However, in their response (June 30, 2022), the Applicant proposed to conduct (b) (4) testing following worst-case scenario conditioning, specifically including (b) (4) . In our communication regarding post-marketing commitments (dated July 18, 2022), we requested the Applicant, to commit to perform visual inspection testing following (b) (4) (b) (4)) with a maximum fill volume, using at least a (b) (4) solution, instead of performing (b) (4) testing. We specified that the testing should include, but not be limited to, visual inspection to assess for tears, cracks, and breaks after each (b) (4) . The Applicant agreed to submit this testing and results for our review on or before December 31, 2022.

2. Suspension (hanger eyelet) testing

In our information request (IR) from April 4, 2022, we asked the Applicant to provide suspension (hanger eye let testing). The Applicant replied (April 29, 2022) that this

testing was not performed by the manufacturer and that the FEP (b) (4) meets the FEP (b) (4) meets (b) (4) with (b) (4). In our follow-up IR (dated May 13, 2022), we communicated to the Applicant that the (b) (4) criterion of the (b) (4) FEP (b) (4) might not be applicable to the parts of the bags nearing the (b) (4), which may have different mechanical properties than the (b) (4). Therefore, we requested again suspension (hanger eyelet) testing of the (b) (4) to show that this container closure, especially around the (b) (4), is safe when used as intended. In their response from May 20, 2022, the Applicant proposed to provide the testing by July 15, 2022. We replied on June 10, 2022, asking that they provided the testing on June 30, 2022, to allow for sufficient review time. On June 30, 2022, the Applicant provided hanger eyelet testing conducted according to (b) (4). Specifically, the testing was illustrated as follows:

The (b) (4) bags were filled with (b) (4) cryopreservation media (b) (4) as a surrogate to the final drug product as it is the drug product formulation solution. The bags were packaged within metal cassettes, cryopreserved, and then (b) (4) (b) (4), (b) (4)

Furthermore, to account for the longest acceptable administration time, all bags were subjected to (b) (4) (b) (4) (b) (4)

(b) (4)

None of the bags fell. Photographs were taken and (b) (4) were compared to the control bag – some stretching was evident with time progression, but (b) (4) around the eyelet is still intact and remained functionally intact throughout testing. There were no protocol deviations. This testing and results are acceptable.

3. (b) (4) Testing (Post Marketing Commitment)

To our request to provide (b) (4) testing (April 4, 2022), the Applicant responded that (b) (4) studies performed with the cryoshipper (where the (b) (4) is contained in the overwrap and cassette) showed that the no damage to the (b) (4) was identified. However, this testing does not demonstrate that the (b) (4) can withstand (b) (4) when used on its own (i.e., without the overwrap and the cassette and the cryoshipper). Therefore, we requested the Applicant, to commit to perform (b) (4) testing of the filled (b) (4) (filled to nominal capacity) as a post-marketing commitment. We suggested the Applicant could use (b) (4) as guideline, and provide justifications for the test method, results, and conclusions as part of a complete test report. We asked that the results for this (b) (4) testing on the (b) (4) bag be submitted for our review on or before December 31, 2022.

4. Capacity testing

In our information request from April 4, 2022, we asked the Applicant to provide capacity testing (including (b) (4) testing) to demonstrate that the (20 mL) volume that they propose is appropriate for the (b) (4) size that they propose in this submission. The Applicant provided a response to this request, on April 29, 2022, stating that the capacity testing was not performed by the manufacturer of the bag (b) (4)) and that the nominal volume of the product is 20 mL whereas the maximum fill volume of the (b) (4) is (b) (4). On May 9, 2022, the review team discussed that the given the maximum fill capacity is significantly larger than the DP volume, the capacity testing can be waived for the purpose of this BLA.

5. (b) (4) Testing

In the document titled (b) (4) -memo.pdf, (attachment 9, starting on page 105 of 121), the manufacturer (b) (4)) provided the protocol and the interim report for (b) (4) testing. This testing will be completed with (b) (4) manufactured batches of the bags (b) (4) . This bag is constituted of FEP (same as the (b) (4)). The manufacturer reported that all acceptance criteria were met for the (b) (4) batch tested. The testing planned and the preliminary results are acceptable.