

CBER Facility/CMC BLA Review Memorandum

BLA STN 125755/0

Product Name: Skysona (elivaldogene autotemcel, eli-cel)

Wei Wang, Ph.D./Microbiologist/OCBQ/DMPQ/B3

1. **BLA#:** STN 125755/0

2. **APPLICANT NAME AND LICENSE NUMBER**

bluebird bio, Inc. (abbreviated as bluebird) US License # 2160

3. **PRODUCT NAME/PRODUCT TYPE**

USAN: elivaldogene autotemcel, eli-cel

Proprietary Name: Skysona

Other names: Lenti-D Drug Product, PC702

4. **GENERAL DESCRIPTION OF THE FINAL PRODUCT**

- a. **Pharmacologic Class:** eli-cel is genetically modified autologous CD34+ cell-enriched population that contains hematopoietic stem cells (HSCs) transduced ex vivo with Lenti-D lentiviral vector (LVV) encoding adenosine triphosphate [ATP]-binding cassette subfamily D member 1 (ABCD1) complementary deoxyribonucleic acid (cDNA) for human adrenoleukodystrophy protein (ALDP).
- b. **Dosage form:** Suspension for intravenous infusion
- c. **Strength/Potency:** Between $\times 10^6$ and 30×10^6 cells/mL
- d. **Route of administration:** Intravenous infusion
- e. **Indication(s):** eli-cel is indicated for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy who do not have a willing and available human leukocyte antigen (HLA)-matched sibling hematopoietic stem cell (HSC) donor.

5. **MAJOR MILESTONES**

First Committee Meeting	November 8, 2021
Filing Meeting	December 2, 2021
Pre-license Inspection	February 14 – 18, 2022
Mid-cycle Meeting	May 19, 2022
Late-cycle Meeting	June 30, 2022
Advisory Committee Meeting	June 9 – 10, 2022
PDUFA Action Date	September 17, 2022

6. **CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Wei Wang/OCBQ/DMPQ/B3	Manufacturing facilities, equipment and CMC (Sections 3.2.S, 3.2.P, and 3.2.A.1)

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
None		N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
9/23/2021	STN 125755/0.1 (part 2 of 2)	Module 3, Reviewed
8/17/2022	STN 125755/0.93 (PMC)	Module 1, Reviewed

9. Referenced REGULATORY SUBMISSIONS (including IND and Master File)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BB-MF (b) (4)	(b) (4)	Type V Master File, Manufacturing and Laboratory Facilities and Quality Systems	Yes	No DMF review required, information pertinent to manufacturing facility is provided in the BLA
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to Office of Tissues and Advanced Therapies (OTAT) reviewers
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OTAT reviewers
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA.
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OTAT reviewers

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OTAT reviewers
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OTAT reviewers
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
BBMF (b) (4)	(b) (4)	(b) (4)	Yes	Defer to OTAT reviewers
MF (b) (4)	Lonza Houston Inc.	Lonza Houston Cell and Gene Therapy Manufacturing Facility	Yes	No DMF review required, information pertinent to manufacturing facility is provided in the BLA
STN (b) (4)	(b) (4)	(b) (4)	Yes	No DMF review required, information pertinent to container closure is provided in the BLA

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The applicant submits this BLA, STN 125755/0, for its new gene therapy product eli-cel for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy who do not have a willing and available human leukocyte antigen (HLA)-matched sibling hematopoietic stem cell (HSC) donor.

The drug substance (DS) critical component, Lenti-D LVV, is manufactured at the (b) (4) site (abbreviated as (b) (4), FEI (b) (4), and eli-cel DS and drug product (DP) are manufactured at the Lonza Houston, Inc., TX site (abbreviated as LHI, FEI #3013629214).

The manufacturing of Lenti-D LVV was covered in a surveillance inspection of (b) (4) by the Office of Regulatory Affairs (ORA) in (b) (4) per DMPQ request.

This inspection of (b) (4) was classified as Voluntary Action Indicated (VAI) and all observations listed in the Form FDA 483 have been resolved.

CBER performed the pre-license inspection (PLI) of the LHI facility in February 2022 for the manufacture of eli-cel (and beti-cel under the other BLA 125717/0 from the applicant) DS and DP. No Form FDA 483 was issued at the end of this PLI, and the inspection was classified as No Action Indicated (NAI).

This review memo covers areas including Chemistry and Manufacturing Controls (CMC) with focus on microbial controls, and facility with focus on facility and major equipment qualification, cleaning, environmental monitoring and controls of cross-contamination.

Based on review of this BLA submission and amendment which addressed the DMPQ information request, and the outcome of inspections of the manufacturing facilities, approval of this BLA is recommended.

B. RECOMMENDATION

I. APPROVAL

Based on information reviewed in this submission, approval is recommended with one post-approval commitment from DMPQ. The applicant commits to provide the sensitivity of a (b) (4) (b) (4) method by February 28, 2023. Under this license, bluebird is recommended for approval to manufacture the DS component, Lenti-D LVV, at (b) (4) the eli-cel DS, the final formulated eli-cel DP, filling, labelling, and packaging at Lonza Houston, Inc., Houston, TX, US.

II. COMPLETE RESPONSE (CR)

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Wei Wang, Ph.D./Microbiologist OCBQ/DMPQ/B3	Concur	
Jie He, Team Lead OCBQ/DMPQ/B3	Concur	
Carolyn Renshaw, Division Director OCBQ/DMPQ	Concur	

Review of CTD

Table of Tables

Table 1. Lenti-D LVV Manufacturing, Testing, and Storage Sites 5

Module 3

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3.2.S.2.2 Description of Manufacturing Process

Manufacturing Process Steps

Table 3 summarizes the Lenti-D LVV manufacturing process steps along with the information of manufacturing equipment and manufacturing rooms.

Table 3. Overview of Lenti-D LVV Manufacturing Process, Facility and Equipment

(b) (4)

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

(b) (4)

3.2.P DRUG PRODUCT

eli-cel consists of autologous CD34+ cell enriched population that contains hematopoietic stem cells transduced with Lenti-D LVV carrying human ATP-binding cassette subfamily D member 1 (ABCD1) cDNA-derived sequences that encode human adrenoleukodystrophy protein (ALDP).

Review Comments: DMPQ defers to OTAT reviewers to evaluate the following Sections, except for the study of the container closure integrity test (CCIT), and 3.2.P.2.5 are reviewed by both OTAT and DMPQ:

- 3.2.P.1 *Description and Composition of the Drug Product*
- 3.2.P.2 *Pharmaceutical Development*
 - 3.2.P.2.1 *Components of the Drug Product*
 - 3.2.P.2.2 *Drug Product – Formulation, Overages, Physicochemical and Biological Properties*

- 3.2.P.2.3 *Manufacturing Process Development*
- 3.2.P.2.4 *Container Closure System (CCS) – DMPQ defers to OTAT to review (i) CCS suitability with respect to materials of construction, protection from moisture, light, oxygen, and adsorption of the Drug Product to the container, (ii) E&L studies and data as it pertains to safety and product quality.*
- 3.2.P.2.5 *Microbiological Attributes – eli-cel is comprised of living cells and is manufactured under aseptic conditions. All container-closure components and excipients are verified to be sterile before use. DP lot release testing includes (b) (4) methods for safety, sterility and endotoxin samples are aseptically obtained from the final container (b) (4) of the DP bag. The DP is stored frozen and does not contain preservatives. The final eli-cel container is a fluorinated ethylene propylene (FEP) (b) (4) bag. Each bag is (b) (4) by the manufacturer, and any (b) (4) result in the bag being rejected. Bags are (b) (4) sterilized by the vendor. Each lot is evaluated for sterility and endotoxin.*
- 3.2.P.2.6 *Compatibility*

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The manufacturing and testing sites for eli-cel are listed in Table 8.

Table 8. Manufacturing and Testing Facilities for the drug Product eli-cel

Facility	Identification Numbers	Responsibility
Lonza Houston, Inc 14905 Kirby Dr. Houston, TX 77047 USA	FEI: 3013629214* DUNS: 832903004	Drug product manufacturing, packaging, labeling; and in-process, release testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release testing and stability testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release testing and stability testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release testing and stability testing

Facility	Identification Numbers	Responsibility
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release and stability testing
(b) (4)	FEI: (b) (4) DUNS: (b) (4)	Drug product release and stability testing

*PLI of this site was performed 2/14/2022 to 2/18/2022, and the PLI was classified as No Action Indicated (NAI).

**PLI of this site was waived. The Inspection Waiver memo was uploaded to CBER Connect on (b) (4)

Review Comments: DMPQ defers to OTAT to review the following sections:

- 3.2.P.3.2 Batch Formula
- 3.2.P.3.3 Description of Manufacturing Process – also see Table 4 of this review memo.
- 3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.5 Process Validation and/or Evaluation

Review Comments: The applicant summarized the testing results for the (b) (4) PPQ lots of eli-cel. The data under the DMPQ purview met specifications (e.g., PPQ batch analyses results, including Sterility: No Growth, and Endotoxin: (b) (4) DMPQ defers to OTAT to perform comprehensive review of Process Validation and/or Evaluation and testing results of additional operational parameters during the manufacture of eli-cel PPQ lots.

Aseptic Process Simulation

Review comments: The following APS documents were submitted in this BLA 125755/0 for eli-cel and in the BLA 125717/0 for beti-cel (FDA approved on 8/17/2022):

(b) (4)

(b) (4)

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(b) (4)

Shipping Validation

Review Comment: The following shipping validation documents (protocols and reports) were also submitted in the BLA 125717/0 for beti-cel (FDA approved on 8/17/2022).

The applicant provided the following shipping validation protocols and qualification reports:

- PRCL-0121: $\leq -140^{\circ}\text{C}$ Cryoshipper Validation Project Plan. This shipping qualification protocol outlined the user requirements (Table 10).

(b) (4)

(b) (4)

(b) (4)

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(b) (4)

DMPQ defers to the OTAT reviewer to evaluate the following shipping qualification documents regarding if the shipping conditions have any impact to the product quality:

(b) (4)

3.2.P.4 Control of Excipients to 3.2.P.6 Reference Standards or Materials

Review Comments: DMPQ defers to OTAT to review the following sections, except release testing results of sterility and endotoxin:

- 3.2.P.4 Control of Excipients
 - 3.2.P.4.1 Specifications
 - 3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures
 - 3.2.P.4.4 Justification of Specifications
 - 3.2.P.4.5 Excipients of Human or Animal Origin
 - 3.2.P.4.6 Novel Excipient
- 3.2.P.5 Control of Drug Product
 - 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s).
 - 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures. Noted, bluebird used a validated (b) (4) method to evaluate the final drug product container closure integrity (CCI) of the (b) (4) bag under normal use and DP transportation and storage conditions (see Section 3.2.P.7 for review of CCIT under the DMPQ purview). DMPQ defers to OTAT device review team to further evaluate additional tests required for the (b) (4) bag.
- 3.2.P.5.4 Batch Analyses – The release testing results (e.g., Sterility and Endotoxin) under the DMPQ purview all met pre-defined acceptance criteria of Sterility (No Growth) and Endotoxin (b) (4) per kg patient weight, or (b) (4) DMPQ defers to OTAT reviewer to evaluate the adequacy of these specifications.
- 3.2.P.5.5 Characterization of Impurities

- [3.2.P.6 Reference Standards or Materials](#)

3.2.P.7 Container Closure System

The container closure system for eli-cel consists of a primary package container (i.e., (b) (4) Cryopreservation bag), a secondary package container (b) (4) Overwrap bag), and a tertiary package container (a metal cryo-cassette).

Review Comments: The DP (b) (4) bag for eli-cel is the same as that for beti-cel (under BLA 125717/0, FDA approved on 8/17/2022).

Primary Packaging

The primary container closure for eli-cel is the (b) (4), a 20-mL fluorinated ethylene propylene (FEP) cryopreservation bag, manufactured by (b) (4). In Section 3.2.P.7 of STN 125755/0.1, bluebird provided specifications and technical information as well as representative drawing of the (b) (4) bag.

The applicant stated the following:

- The (b) (4) bag has been demonstrated to meet (b) (4) Class (b) (4) requirements.
- (b) (4) bags are manufactured under cGMP in an ISO (b) (4) clean room and are (b) (4) tested with (b) (4).
- The bags are (b) (4) sterilized by the manufacturer using a (b) (4) sterilization cycle (b) (4) that is validated to achieve a sterility assurance level (SAL) of (b) (4).
- (b) (4) bags are accepted for use at the eli-cel manufacturing site based on visual inspection and review of vendor certificates for SAL (b) (4).
- Sterility (Acceptance criteria: no growth) and endotoxin (acceptance criteria: (b) (4)) testing are performed on (b) (4) from each lot received.

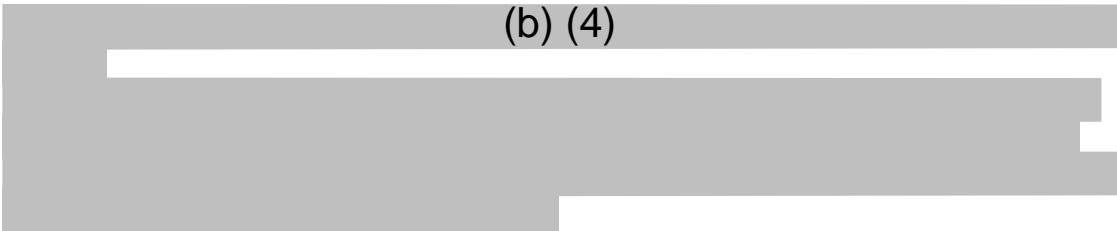
Container Closure Integrity Test

The applicant stated that the container closure integrity (CCI) of the (b) (4) bags was tested and confirmed and provided the following documents in Section 3.2.P.2 of STN 125755/0.1:

- VAL-VEN-PRCL-0084: *Container Closure Integrity Test*: (b) (4). This CCIT protocol outlined the following:


(b) (4)

(b) (4)




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(b) (4)



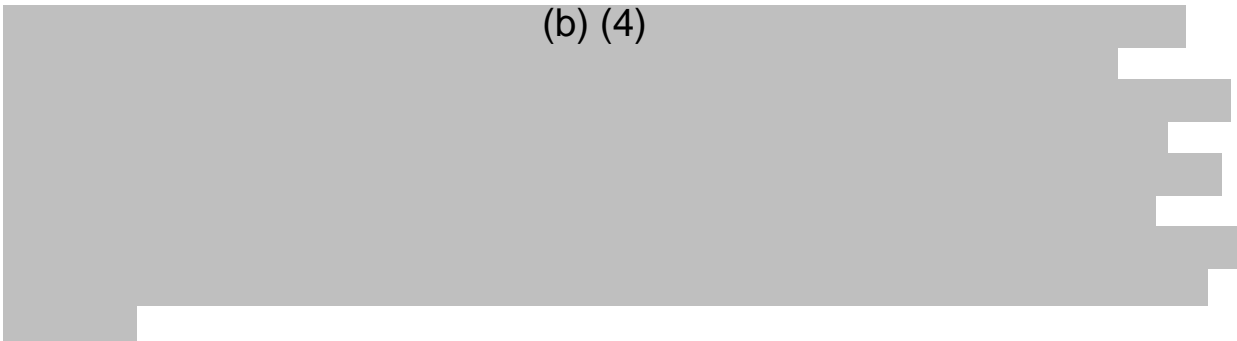
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Post-Marketing Commitment

The following post-marketing commitment (PMC) item was sent to bluebird on 8/15/2022, and the applicant's response (STN 125755/0.93) was received on 8/17/2022:

CBER requests that you make the following post-marketing commitment:

Sensitivity of the (b) (4) method PMC

bluebird bio, Inc., commits to establish the sensitivity of (b) (4) method for the (b) (4) bag.

Final Report Submission: February 28, 2023

The Applicant's Response:

bluebird bio, Inc., commits to establish the sensitivity of (b) (4) method for the (b) (4) bag.

Final Report Submission: February 28, 2023

Review Comments: The applicant response was acceptable.

3.2.P.8 Stability

Review Comments: The submitted stability data submitted in Section 3.2.P.8.3 Stability Data under the DMPQ purview appeared acceptable, including Sterility (acceptance criteria: No Growth) and Endotoxin (Acceptance criteria: (b) (4))

DMPQ defers to OTAT to evaluate the adequacy of additional stability data and whether the available stability data supports the proposed shelf-life. DMPQ defers to OTAT to review the Section 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment.

3.2.A.1 Facilities and Equipment

Facility and Equipment (b) (4)

Overview

(b) (4)

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

(b) (4)

Facility and Equipment (LHI)

Major Equipment Overview

LHI is contracted by the applicant to manufacture beti-cel and eli-cel DS and DP. The LHI facility consists of (b) (4)

The receiving of raw materials and storage of final drug products are performed in the warehouse in (b) (4)

The major equipment used for manufacturing of eli-cel are listed in Table 4, including (b) (4)

The Installation and Operational Qualification (IQ/OQ) reports were reviewed for the major equipment during the PLI of LHI. The performance re-qualification for the product autoclave was also reviewed during the PLI.

HVAC System and Utilities

The HVAC system performance has been established to maintain controlled environmental conditions through IQ/OQ of (b) (4) manufacturing suites, (b) (4). The HVAC system was covered during the PLI, including review the recent HVAC and High Efficiency Particulate (Air HEPA) filter re certification reports. Briefly,

(b) (4)

LHI does not have a water system for manufacturing process. LHI purchases WFI for (b) (4) purposes.

The vendors maintain Certificate of Analysis (CoA) for all (b) (4) and provides evidence of the passing results. (b) (4) are tested by the vendor for (b) (4) (assay) prior to shipment to LHI. Upon receipt of the (b) (4) at LHI, (b) (4) testing of the (b) (4) and review of the CoA is performed as part of the material release process. Following release, the (b) (4). The frequency testing of (b) (4) is every (b) (4) for (b) (4) as per procedure.

(b) (4) only utilizes the (b) (4) supplied from a (b) (4) distribution system located in (b) (4), and (b) (4) is used for the manufacture of bluebird's products.

(b) (4) is supplied from (b) (4) through (b) (4) types of alarms (b) (4) will signal (b) (4). A centralized system delivers (b) (4) to the points of use located in manufacturing suites and laboratory. The (b) (4) of the manufacturing processes.

Clean steam is produced from steam generators. The steam generators are supplied with (b) (4) water. Clean steam is distributed within the facility manufacturing areas for (b) (4) use. The use of a (b) (4) 316L stainless steel steam generators feeding (b) (4). Clean steam quality and clean steam (b) (4) are routinely monitored and tested.

During the PLI, the LHI subject matter expert (SME) stated (b) (4) is used for the manufacture of bluebird's products.

The liquid nitrogen (LN₂) is supplied and maintained by vendors. The LN₂ is stored and supplied from an (b) (4). The level is monitored and maintained by external industrial supplier. The LN₂ is supplied (b) (4)

The (b) (4) LN₂ points of use in the (b) (4) are fed from (b) (4) connected at each point of use. All LN₂ (b) (4) are monitored for temperature by the (b) (4) continuous monitoring system. The (b) (4) system is configured with an alarming function. Both temperature (b) (4) are identified locally at the equipment with local alarming function.

Prevention of Contamination and Cross-Contamination

Prevention of contamination and cross-contamination is achieved through the facility design features and the application of LHI's control and operational measures used in the facility.

Facility Design: The following facility features are designed to prevent contamination and cross-contamination:

(b) (4)

Procedural Controls: Following procedures are in place to prevent contamination and cross-contaminations:

(b) (4)

- Closed systems: All process operations are performed using closed systems utilized to protect the product from contamination, and to protect the environment from product contamination. Any open manipulations are performed in (b) (4).
- Gowning and aseptic manipulation training (AMT): Personnel must take gowning training, AMT, and pass aseptic personnel qualifications prior to perform any aseptic manipulations per Lonza SOP USHT-3875: *Lonza Houston Aseptic Simulation Program*.
- Single use technology: Single-use, pre-sterilized disposable materials are used in the process to minimize the chance of cross- contamination between products.
- Changeover: Between production campaigns, rooms undergo product changeover cleaning and a formal line clearance verified by Quality Assurance (QA). Room changeover includes removal of product dedicated equipment, cleaning of surfaces and non-disposable equipment. The room is then released by QA prior to initiation of the next campaign.
- Facility Cleaning: All surfaces in cleanroom suites, including exterior surfaces of equipment, are routinely cleaned with qualified cleaning agents. Facility cleaning and sanitizations and disinfectant qualifications were reviewed during the PLI of LHI and were found acceptable.

Environmental Monitoring

EM is performed to ensure the facility is operating within a state of microbial control. All manufacturing activities at LHI take place in the appropriate class of environment following the established guidelines and requirements

Lonza SOP USWV-30403: *Central Environment Monitoring Procedure* governs the EM program in LHI. Each cleanroom suite (e.g., (b) (4)) has its own EM program to specify sampling locations, frequencies, and alert and action limits. Action levels are driven by (b) (4), and FDA Aseptic Processing of Biological Products Guidance.

Review Comments: The submitted facility floor maps, flow diagrams, HVAC zoning maps, and cleanroom classifications appeared acceptable. Furthermore, CBER (DMPQ and OTAT) conducted a PLI of the LHI (FEI: 3013629214) from 2/14/2022 to 2/18/2022 in support of two BLAs, STNs 125717/0 (beti-cel) and 125755/0 (eli-cel).

The PLI of Lonza Houston facility was conducted per Compliance Program Guidance Manual-45 Biological Drug Products 7345.848. The equivalent of a Level I inspection covered the following systems (see EIR for details):

- *Quality, including review of Quality Manual, Deviation and CAPA procedures, change control procedure.*
- *Facility and Equipment, including review of qualification HVAC systems, EMPQ of (b) (4), computerized budling management systems, EM programs, facility and equipment cleaning procedures, major equipment qualifications, flows*

of personnel, materials, DP samples, and waist. Noted, personnel and material flow in (b) (4)

- *Materials, including review of raw material receiving and testing, quarantine, storage and distribution, inventory controls, prevention of mix-up. Noted, the LHI stated (b) (4).*
- *Production, including review of APS study report, batch record of the process validation lots, smoke study in (b) (4), and observation of DP manufacturing steps (e.g., formulation, filling, labeling and visual inspection). Noted, (b) (4) (b) (4) manufactured in a cleanroom suite (b) (4) and associated production areas (e.g., visual inspection and packaging areas) at a given time.*
- *Packaging and Labelling*
- *Laboratory Control.*

The PLI included walkthrough inspection of the facility, observation of portions of manufacturing operations, and review of various documents, records and reports including those related to facility and equipment qualification, validation, batch records, training, laboratory, change control, deviation reports, and Corrective and Preventive Action (CAPA). No FDA Form 483 was issued at the end of this PLI. However, discussion items were conveyed to the Lonza Houston management in daily wrap-up meetings and in the final close out meeting (see General Discussions with Management section of EIR).

3.2.R Regional Information (USA)

Review Comments: *DMPQ defers to OTAT to review following documents:*

- *Executed Batch Records*
- *Method Validation Package*
- *Combination Products: N/A*
- *Comparability Protocols: N/A*