

CBER DMPQ CMC/Facility BLA Review Memorandum

BLA 125758/0

atidarsagene autotemcel, OTL-200; autologous CD34+ HSPCs transduced ex vivo with a replication-incompetent lentiviral vector encoding human arylsulfatase A (ARSA)/ Lenmeldy

Viviana Ramirez, Reviewer, MRB2/DMPQ

1. BLA#: STN 125758/0**2. APPLICANT NAME AND LICENSE NUMBER**

Orchard Therapeutics (Europe) Limited (License # 2263)

3. PRODUCT NAME/PRODUCT TYPE

Proper Name: atidarsagene autotemcel, OTL-200; autologous CD34+ hematopoietic stem and progenitor cell (HSPCs) transduced ex vivo with a replication-incompetent lentiviral vector encoding ARSA

Proprietary Name: Lenmeldy

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

- a. Pharmacological category: **Gene Therapy**
- b. Dosage form: **Suspension**
- c. Strength/Potency: **2 - ^{(b)(4)} × 10⁶ cells per mL**
- d. Route of administration: **Intravenous infusion**
- e. Indication(s): **Treatment of pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD)**

5. MAJOR MILESTONES

- Application receipt date: July 19, 2023
- First Committee Meeting: August 3, 2023
- Filing Meeting: September 05, 2023
- Filing Action: September 15, 2023
- Mid-Cycle Meeting (Internal): November 2, 2023
- Mid-Cycle Communication: November 17, 2023
- Internal Late Cycle Meeting: December 15, 2023
- Action Due Date (ADD): March 18, 2024

6. DMPQ CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Viviana Ramirez, OCBQ/DMPQ/MRB2	CMC/Facilities

7. INTER-CENTER CONSULTS REQUESTED

No inter-center consults were requested.

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments
07/19/2023	STN 125758/0 (eCTD 0000)	Original BLA submission including sections in modules 1, 2 and 4
02/27/2024	STN 125758/0 (eCTD 0050)	Container Closure Integrity Testing Information Request #1
03/08/2024	STN 125758/0 (eCTD 0056)	Sterile filtration of (b) (4) [REDACTED] Information Request #2

9. REVIEWER SUMMARY AND RECOMMENDATION**A. EXECUTIVE SUMMARY**

Orchard Therapeutics Europe Limited (Orchard) submitted BLA STN 125758/0 BLA for the licensure of atidarsagene autotemcel, OTL-200; autologous CD34+ HSPCs transduced ex vivo with a replication-incompetent lentiviral vector encoding human arylsulfatase A (ARSA)/ Lenmeldy, intended for treatment of pediatric patients with pre-symptomatic late infantile (PSLI), pre-symptomatic early juvenile (PSEJ) or early symptomatic early juvenile (ESEJ) metachromatic leukodystrophy (MLD). CBER/DMPQ reviewed and evaluated the drug substance (DS) and drug product (DP) manufacturing processes and facilities proposed for use in the manufacture of Lenmeldy. Information reviewed, evaluated, and documented in this memo includes data to validate and support the consistency of the manufacturing process and product quality; facility information which includes utilities, cross-contamination prevention measures, and maintenance of controlled environments; and equipment for use in the manufacturing (all product-contact equipment used in DS and DP manufacturing are single-use).

The DS manufacturing site, AGC Biologics S.p.A., completed validation and qualification activities that included but were not limited to process, container closure integrity testing (CCIT) of (b) (4), environmental monitoring performance testing, and qualification of the (b) (4) including validation of the disinfection/decontamination process. The facility is designed for the prevention and control of contamination and cross-contamination with many engineering and procedural controls in place, including single-use product-contact components. The overall control strategy supports sterility assurance and consistency of manufacturing.

The drug product manufacturing site is the same as the DS manufacturing site, AGC Biologics S.p.A., completed validation and qualification activities that included but were not limited to process, aseptic process media simulation studies, CCIT, environmental monitoring performance testing, and qualification of the (b) (4), including validation of the disinfection/decontamination process. The facility is designed for the prevention and control of contamination and cross-contamination with many engineering and procedural controls in place, including single-use product-contact components and (b) (4) technology. The overall control strategy supports sterility assurance and consistency of manufacturing.

A pre-license inspection (PLI) of AGC Biologics S.p.A. was conducted from November 8, 2023 to November 20, 2023. An FDA-483, Inspectional Observations form, was issued for: deficient aseptic practices, failure to adequately investigate deviations, and failure to justify freezer qualification load selections. The inspection was classified as Voluntary Action Indicated (VAI).

B. Recommendation

I. APPROVAL

Approval is recommended based on the review of the information submitted to BLA 125758/0 including information provided in the corresponding amendments and the inspectional compliance history evaluations and with the following Post-Marketing Commitments (PMC):

1. Orchard Therapeutics (Europe) Limited commits to submit a container closure integrity test (CCIT) study to demonstrate the integrity of the (b) (4) with the inclusion of a positive control with (b) (4). The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by December 31, 2024.
2. Orchard Therapeutics (Europe) Limited commits to perform validation of the (b) (4) used for the (b) (4) that are utilized in the aseptic manufacturing process of the OTL-200 DP drug product, in addition to performing (b) (4) testing. The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by September 30, 2024.

Additionally, the following inspectional consideration for the next inspection is recommended. The inspectional consideration is part of the standard scope of inspection. CBER understands that the consideration may or may not be taken (based on risk and available resources) and is not requesting documentation to be submitted as evidence of completion.

- (b) (5), (b) (7)(E)

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Viviana Ramirez, CMC / Facility Reviewer, OCBQ/DMPQ/MRB2	Concur	
Anthony Lorenzo, Branch Chief, CBER/OCBQ/DMPQ/MRB2	Concur	
Carolyn Renshaw, Director, CBER/OCBQ/DMPQ	Concur	

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Module 3

3.2.S Drug Substance: (b) (4)

(b) (4)

(b) (4)

[Redacted]

[Redacted]

- [Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

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

(b) (4)

3.2.P DRUG PRODUCT: OTL-200 Suspension for Intravenous Infusion

3.2.P.1 Description and Composition of the Drug Product

The cryopreserved DP, OTL-200 Suspension for Intravenous Infusion, is intended for intravenous administration. OTL-200 DP is for autologous use only. OTL-200 DP is a cryopreserved product supplied in one or more sterile, single use 50 mL nominal volume (b) (4) bag(s) for administration and is formulated in cryopreservation formulation medium (5% v/v DMSO, (b) (4)). CD34+ cells are resuspended at a target concentration of 2 to 2×10^6 viable cells per mL in a volume of 10 to 20 mL of cryopreservation formulation medium per (b) (4) bag. The cryopreserved DP is infused to the patient after thawing.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all OTL-200 DP manufacturing facilities.

3.2.P.3.3 Description of Manufacturing Process

Preparation of the Media

(b) (4)

(b) (4)

Freezing Medium Preparation (Final Composition of (b) (4)
+ 5% (v/v) DMSO)

(b) (4)

(b) (4)

(b) (4)

Step (b) (4): Formulation and fill

Based on the viable cell concentration determined in Step (b) (4) the cell suspension is adjusted to a target concentration of $2 - (b) (4) \times 10^6$ viable cells/mL in a final formulation containing (b) (4) + 5% (v/v) DMSO. (b) (4)

(b) (4)

A visual inspection is performed on the final filled container by the operator to confirm the appearance of the cell suspension and integrity of the primary package, *i.e.*, 50 mL (b) (4) cryobag(s). (b) (4)

After the visual inspection is performed, the filled (b) (4) cryobag(s) are labelled. Each primary 50

mL (b) (4) cryobag is placed in a secondary (b) (4) overwrap bag and labelled in a Grade (b) (4) (ISO (b) (4) room. This secondary overwrap bag is sealed in a (b) (4).

Upon final formulation, packaging, and labelling, the DP and QC samples are transferred to the (b) (4) and cryopreserved using the same (b) (4). After cryopreservation, each frozen DP bag is placed into a labelled metal cassette and stored at <-130°C in the vapor phase of liquid nitrogen.

Batch size: The final DP volume is variable from a minimum of 10 mL to a maximum of (b) (4) mL per batch containing a target concentration of $2 - (b) (4) \times 10^6$ viable cells per mL.

Reviewer's Assessment: Adequate information is provided for the DP process description. Description and assessment of controls associated with critical steps operating and performance parameters, in-process controls and hold-times are provided in sections 3.2.P.3.4 Controls of Critical Steps and Intermediates, and 3.2.P.3.5 Process Validation. An inspectional follow-up recommendation (b) (5), (b) (7)(E)

3.2.P.3.4 Controls of Critical Steps and Intermediates

The microbial control strategy for OTL-200 DP is as described for OTL-200 Drug Substance (DS) in 3.2.S.2.4, (b) (4). Visual assessment is performed on the final filled container and (b) (4).

Reviewer's Assessment: Microbial control strategy including sterility assurance steps and in-process control testing appears suitable. Maximum in-process hold times for each process step have been identified. Evaluation of all other maximum allowable hold time studies is deferred to OTP reviewers. Validation of aseptic filling is reviewed in section 3.2.P.3.5.

3.2.P.3.5 Process Validation and/or Evaluation

(b) (4) batches of (b) (4) DP were produced from mobilized Peripheral Blood (mPB), each batch collected from a single healthy donor. The volume of mPB used for production of each of the PPQ batches was approximately (b) (4) mL; this is consistent with the volume expected for patient treatment. (b) (4) PPQ batches were executed in one campaign, comprising enrichment of CD34+ cells from fresh mPB, transduction with ARSA LVV, and formulation and filling of the DP. Each batch was formulated, filled, and cryopreserved to generate the (b) (4) OTL-200 batches. (b) (4)

PPQ Batch Details

Batch Number	(b) (4), (b) (6)
ARSA Vector Lot	(b) (4)
End Date of	
Manufacturing	

Release testing included endotoxin (acceptance criteria: (b) (4)) and sterility testing (acceptance criteria: negative). All lots met acceptance criteria.

Aseptic Processing Simulation

The media fill procedure was executed under an AGC Biologics internal media fill protocol MF22. This MF22 process is considered relevant to the OTL-200 manufacturing process as it simulates what is considered the worst-case scenario of processes for OTL-200 including additional manual steps related to (b) (4) which contain additional aseptic manipulations.

The batch size for MF22 covers the simulation of aseptic DP manufacturing processes for OTL-200. MF22 was carried out simulating all the operations that are performed during the different phases of the production process in worst case conditions in terms of the volume, number of operations and manipulations performed, the format of the disposable materials, the types of closure, the internal diameter of the containers and the number of operators. The output of aseptic process simulation are cryobags each containing (b) (4) for a combined total of (b) (4) .

(b) (4)

Acceptance criteria for the aseptic process validation were as follows:

(b) (4)

For initial qualification, three initial media fill runs were performed in each room at AGC Biologics Bresso used to manufacture OTL-200 (b) (4) DP as per the standard protocol using (b) (4) . No growth was observed in any of the samples from any of the media fills, and growth promotion tests met; all the acceptance criteria were met.

Summary of Media Fills

(b) (4)

(b) (4)

Summary of Media Fills: (b) (4) System

(b) (4)

Reviewer's Assessment: The validation design appears to be suitable and all critical process parameters, in-process controls and release tests under DMPQ purview were met. (b) (4)

(b) (4)

Shipment Validation of OTL-200 DP

Shipping of the final cryopreserved DP from the OTL-200 site of manufacture to the DP Administration Site has been validated. The cryopreserved OTL-200 DP will be shipped at a temperature of < -130°C from AGC Biologics to the DP Administration Site(s) using a validated liquid nitrogen (LN2) (b) (4) shipping container. For the shipment of cryopreserved OTL-200 to the QTC, the (b) (4) (b) (4) shipper is used. The shipping container is supplied by (b) (4)

The (b) (4) shipper has established data available from the manufacturer, validating temperature control at : (b) (4)°C for (b) (4) when exposed to (b) (4) simulated temperature conditions. Additionally, the packaging has passed the standards of the U.S. Department of Transportation's title 49 Category B Infectious substance CFR; Section 173.199 and structural integrity testing have been performed.

Summary of (b) (4) Shipper Validation for (b) (4) by Vendor

Study	Test Parameters	Results
(b) (4)		

Study	Test Parameters	Results
(b) (4)		

(b) (4)

(b) (4)

(b) (4)

Reviewer Assessment: The DP shipping validation demonstrated the suitability of the shipment. All acceptance criteria were met. Evaluation of (b) (4) studies is deferred to OTP reviewers.

3.2.P.5 Control of Drug Product

OTL-200 Drug Product is cell suspension formulated in 5% v/v DMSO, (b) (4) and packaged in one or more 50 mL (b) (4) bags. Each batch of OTL-200 must comply with the following microbiological specifications:

Test	Method Principle	Acceptance Criteria
Sterility	(b) (4)	Negative

Test	Method Principle	Acceptance Criteria
Endotoxin (EU/mL)	(b) (4)	(b) (4)

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

Sterility

Sterility is a requirement for a parenteral. The microbiological control test method is performed in compliance with (b) (4) using the (b) (4) system and is specific for the microbiological examination of cell-based products, this method is equivalent to (b) (4). The system uses (b) (4)

Acceptance criterion: Negative.

Bacterial Endotoxin

Endotoxin control is a requirement for a parenteral product and is included in the DP specification. The bacterial endotoxins test is a (b) (4) method performed to (b) (4), and the method is performed according to (b) (4). The endotoxin limit is defined as (b) (4), where (b) (4)

An acceptance criterion of (b) (4) ensures that a patient will not receive (b) (4) as long as no more than (b) (4) is administered. Therefore, infusion of OTL-200 DP will not exceed (b) (4).

Acceptance criterion: (b) (4)

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

Microbiological Examination (Bioburden Testing)

The microbiological control of OTL-200 DP is performed to verify that the suspension shows no microbial growth. This test is performed in accordance with (b) (4) using the (b) (4) system. The system monitors samples to detect the

(b) (4)

Endotoxin

The purpose of this analytical procedure is to verify the absence of bacterial endotoxins. The test is performed according to (b) (4) and to (b) (4).

Reviewer's Assessment: *The firm provided details of the microbiological control (bioburden) and endotoxin testing to support microbial control of the product. The evaluation of the testing performed is deferred to DBSQC.*

3.2.P.5.4 Batch Analyses

The PPQ batches (b) (4), (b) (6) were tested for Bacterial Endotoxins (acceptance criteria: (b) (4)) and Microbiological Control for Cell Suspension (acceptance criteria: negative). All results met acceptance criteria.

Reviewer's Assessment: *Lots included in the batch analyses appear suitable, including the three consecutive DP validation runs.*

3.2.P.7 Container Closure System

OTL-200 is filled into up to eight, single use, 50mL (b) (4) bag(s). Each primary bag is then sealed and packaged into a (b) (4) overwrap (b) (4) bag which is also sealed; the packaged DP is then cryopreserved. The cryopreserved packaged DP is placed in a metal cassette for storage in the vapor phase of liquid nitrogen prior to shipment. The (b) (4) bags used as the primary container for OTL-200 DP ((b) (4)) are intended for (b) (4) of freezing, storage down to (b) (4) °C, and subsequent thawing (at 37°C) of hematopoietic progenitor cells. (b) (4) are 510(k) cleared in the USA (510(k) No. (b) (4)).

Each (b) (4) freezing bag (primary container) consists of one freezing bag with access ports (filling assembly) as the primary containment for hematopoietic progenitor cells and one overwrap bag as secondary containment. Each freezing bag is labelled to facilitate identification. The 50 mL freezing bags used for the OTL-200 DP are also equipped with one eyelet to facilitate suspended placement, e.g., with an infusion rack for administration of the content. To allow visual control of the content, the freezing bags are transparent. The bags are received sterile from the manufacturer.

The manufacturer utilizes (b) (4) for sterilization with a (b) (4) (b) (4). The process is validated for the (b) (4) freezing bags to achieve a sterility assurance level (SAL) of (b) (4). Sterilization is certified in the Certificate of Conformance from the manufacturer.

(b) (4)

(b) (4)

(b) (4)

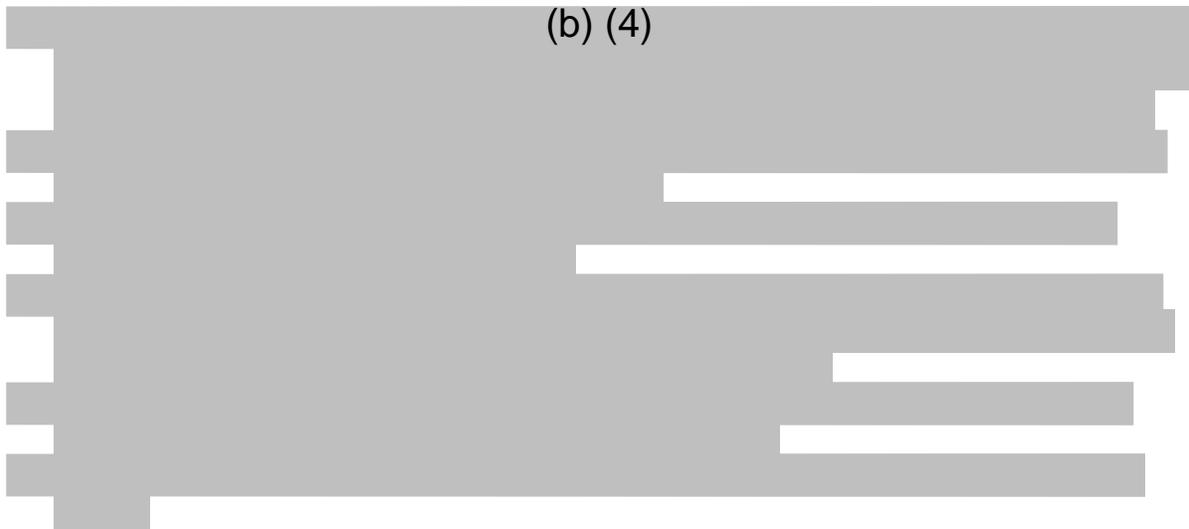
Reviewer Assessment: *The CCIT studies appear inadequate. For the CCIT performed by AGC Biologics, the sensitivity of the positive control in terms of the (b) (4) that could be reliably detected by the method was not provided and the preparation of the positive controls used in the study were not described. Additionally, it is not clear if the positive controls were subjected to the same test conditions as the test samples and if (b) (4) were used in the (b) (4) study.*

It was noted the (b) (4) bags are 510K cleared and that the container closure testing was performed by supplier (b) (4) using modified methods specified in (b) (4). It is not clear if the firm is using the (b) (4) bag as intended under the 510k and if there are differences in the intended use not covered under the 510K. Additionally, the details of the (b) (4) testing performed as per (b) (4), including details of the sensitivity of the positive controls used in the study (i.e., minimum (b) (4) that can be reliably detected by the method) were not provided. An information request was sent 02/15/2024 for clarification of these issues.

The information request was received on 02/27/2024 as amendment STN 125758/0.49 (eCTD 0050).

As part of the response, details were provided about a CCIT performed by Orchard that incorporates the following parameters as recommended by (b) (4) for a probabilistic method:

(b) (4)



(b) (4)

Results are presented in table below. Positive control acceptance criteria were achieved (b) (4), with the positive control showing (b) (4). All results passed and the test article bags were negative for (b) (4) demonstrating the integrity of the (b) (4) cryobags.

Table: Results of Container Closure Integrity Testing of (b) (4) Cryobag - (b) (4)

(b) (4)

Orchard clarified that the FDA 510(k) # (b) (4) states “Intended Use: (b) (4) ” and that the bags are used according to the 510(k) intended use. A summary of (b) (4) Bag Usage was provided and delineated below.

Table: Summary of (b) (4) Bag Usage

FDA 510(k) – Intended Use	Conditions applied for OTL-200	Intended Use Adhered To (Yes/No)
(b) (4)		

As part of container closure integrity testing, modifications were introduced to the (b) (4)

With regards to the challenge testing ((b) (4) testing), Orchard confirmed that the (b) (4) testing performed by the supplier (b) (4) was performed in

accordance with (b) (4) and was not modified. (b) (4) bags for (b) (4) testing were (b) (4) and tested in accordance with (b) (4). A positive control with (b) (4) was not included, however, it was included in the additional CCIT performed by Orchard described above.

Reviewer Assessment: *The additional information regarding container closure integrity testing including the Orchard CCIT study addressed the concerns with the container closure integrity and confirms the suitability of the container. The CCIT study provided by Orchard included a reliable positive control with a (b) (4) that was subjected to the same test conditions including (b) (4) as the test samples. Additionally, the firm confirmed that the (b) (4) bags are utilized as intended under the FDA 510(k) clearance in addition, the supplier (b) (4) performed extensive supporting studies ((b) (4)) that further support the suitability of the bags.*

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Stability testing has been performed following the principles of ICH Q1A and ICH Q5C to support the commercial shelf life. As a cell therapy product, the OTL-200 Drug Product (DP) is stored frozen at <-130°C. As an autologous cell therapy product, each batch of drug product is manufactured for a specific patient and the product is stored while release testing of the patient specific batch takes place and for transport to the clinical site for administration. Stability testing was done on healthy donor batches, which have been shown to be representative of patient batches.

In support of the proposed shelf life, long term stability data on representative batches are presented that show no impact on quality attributes for up to six months when OTL-200 DP, in its commercial configuration, formulation, and cell concentration, is stored frozen in the vapor phase of liquid nitrogen at <-130°C. In-use stability data on representative batches show that OTL-200 DP stored for intervals up to 6 months demonstrate that DP is stable for up to 2 hours post-thaw at room temperature.

The following batches were included in stability studies in support of the commercial shelf life: (b) (4), (b) (6)

The selection of stability batches was intended to demonstrate stability of the DP bracketed across the allowable product concentration range (2×10^6 cells/mL and $(b)^{(4)} \times 10^6$ cells/mL). Stability batches were formulated with both the (b) (4) source of (b) (4) employed for commercial batches and the (b) (4) source of (b) (4) employed during development.

The testing plans for the cryopreserved drug product stability studies include OTL-200 Cryopreserved Drug Product Batch (b) (4), (b) (6) at a Target Concentration of $(b)^{(4)} \times 10^6$

cells/mL microbiological testing at time point 0 and time point 6 months. OTL-200 Cryopreserved Drug Product Batch (b) (4), (b) (6) at a Target Concentration of (b) (4) x 10⁶ cells/mL microbiological testing at time point 0 and time point 6 months. OTL-200 Cryopreserved Drug Product Batches (b) (4), (b) (6) ((b) (4) x 10⁶ cells/mL), (b) (4), (b) (6) (2 x 10⁶ cells/mL) and (b) (4), (b) (6) ((b) (4) x 10⁶ cells/mL) microbiological testing at time point 0 and time point 6 months.

Microbial control testing on all batches (b) (4), (b) (6), (T0 to T=6M) demonstrate that the cryobag container closure system is able to maintain sterility of the drug product stored for a period of 6 months. Stability data have been generated for cryopreserved OTL-200 DP in its commercial configuration, formulation, and concentration at 2 x 10⁶ cells/mL and (b) (4) x 10⁶ cells/mL when stored in the vapor phase of liquid nitrogen at <-130°C for 6 months.

Reviewer’s Assessment: The microbiological testing schedules on the stability study appear acceptable. The results of testing under DMPQ purview support the shelf life of 6 months stored at <-130°C.

3.2.A APPENDICES

Facilities Table

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>Facility: (b) (4)</p> <p>FEI#: (b) (4)</p> <p>Actions: OTL-200 ARSA LVV manufacture, in-process testing, release and stability testing</p> <p>OTL-200 Drug Substance (b) (4) testing</p> <p>OTL-200 Drug Product release/stability testing</p>	<i>Inspection</i>	Yes	Yes	DMPQ performed PLI (b) (4) VAI

Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?*	RMS-BLA entry required?*	Comments
<p>Facility: AGC Biologics S.p.A. Via Antonio Meucci 3, Openzone, Bresso, Milan, Italy 20091</p> <p>FEI#: 3020270660</p> <p>Actions: OTL-200 ARSA release and stability testing</p> <p>OTL-200 Drug Substance manufacture and in-process testing</p> <p>OTL-200 Drug Product manufacture, in-process testing, release and stability testing, primary, secondary, tertiary packaging and storage</p>	<i>Inspection</i>	Yes	Yes	DMPQ performed PLI 11/08- 20/2023
<p>Facility: (b) (4)</p> <p>FEI#: (b) (4)</p> <p>Actions: OTL-200 ARSA LVV release testing</p>	Not required	No	Yes	

List of acronyms:

- ARSA – Human Arylsulfatase A gene
- FEI – Federal Establishment Identifier
- LVV – Lentiviral Vector
- OTL – Orchard Therapeutics Limited
- PLI – Pre-License Inspection
- VAI – Voluntary Action Indicated

AGC Biologics S.p.A

Facility Design

There are two buildings at AGC Biologics facility located (b) (4) apart that are used to manufacture the OTL-200 ARSA LVV and OTL-200 DS and DP. OTL-200 ARSA LVV is manufactured in the (b) (4) building. OTL-200 DS and DP are manufactured in the Bresso building.

(b) (4) Building

The (b) (4) building has been designed and constructed to house: manufacturing areas, raw materials warehouse areas, product storage areas, quality control laboratories, and technical areas. The total area of the site is approximately (b) (4).

(b) (4) is a multi-product manufacturing facility for gene therapy. Types of products manufactured at (b) (4) are summarized below:

- Vector producer cell lines
- Viral vectors: lentiviral vectors, retroviral vectors
- CD34+ transduced cells

The facility is divided into the following main areas:

- Manufacturing areas, including:
 - Production rooms (Grade (b) (4)) (rooms (b) (4))
 - Changing rooms (Grade (b) (4)) (rooms (b) (4))
 - QC testing room (Grade (b) (4)) (room (b) (4))
 - Airlock for waste (Grade (b) (4)) (b) (4)
 - Shared areas (Grade (b) (4)) (corridors, internal warehouses (room (b) (4)), and changing rooms)
- Raw materials Warehouse areas, including:
 - Quarantined/released raw materials at room temperature (rooms (b) (4))
 - Quarantined/released raw materials at (b) (4) °C (cold room (b) (4))
 - Quarantined/released raw materials at (b) (4) °C and (b) (4) °C (rooms (b) (4))
- Product storage areas, including:
 - Quarantined/released products at (b) (4) °C ((b) (4))

The manufacturing areas where OTL-200 ARSA LVV is produced are presented in the table below:

Room Descriptions

Stage of ARSA LVV Manufacturing	Room Number	Room classification	Area Description
(b) (4)			

Stage of ARSA LVV Manufacturing	Room Number	Room classification	Area Description
(b) (4)			

Bresso Building

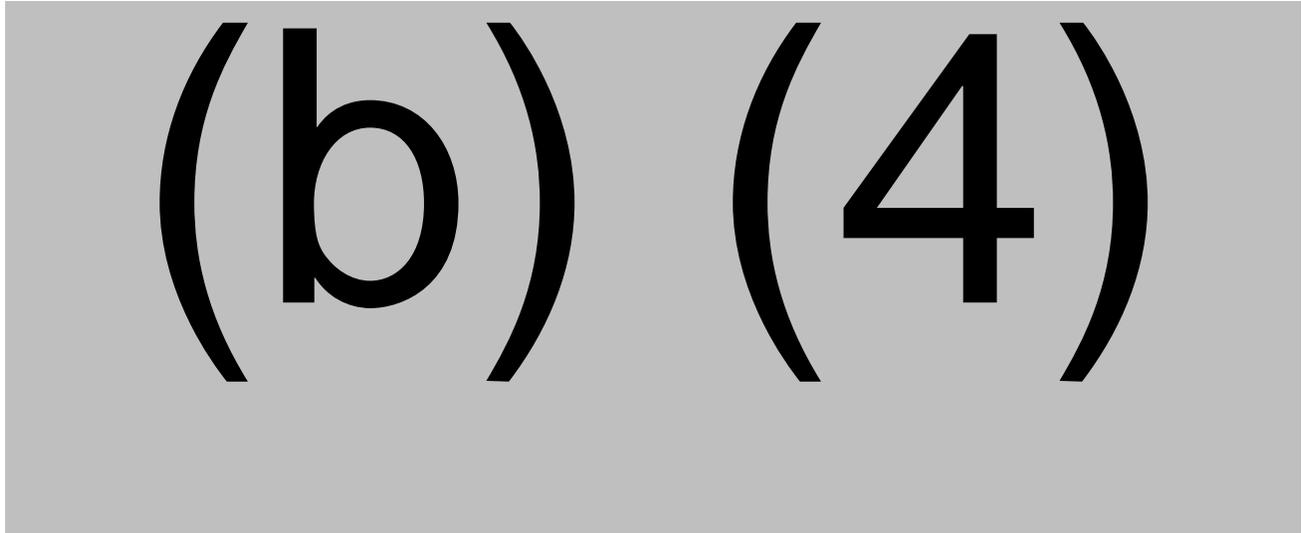
AGC Biologics Bresso facility consists of a total area of about (b) (4) including manufacturing areas, the Quality Control/ Development laboratories and the raw materials warehouse/ products storage areas. The manufacturing areas are described in the table below:

Manufacturing Areas

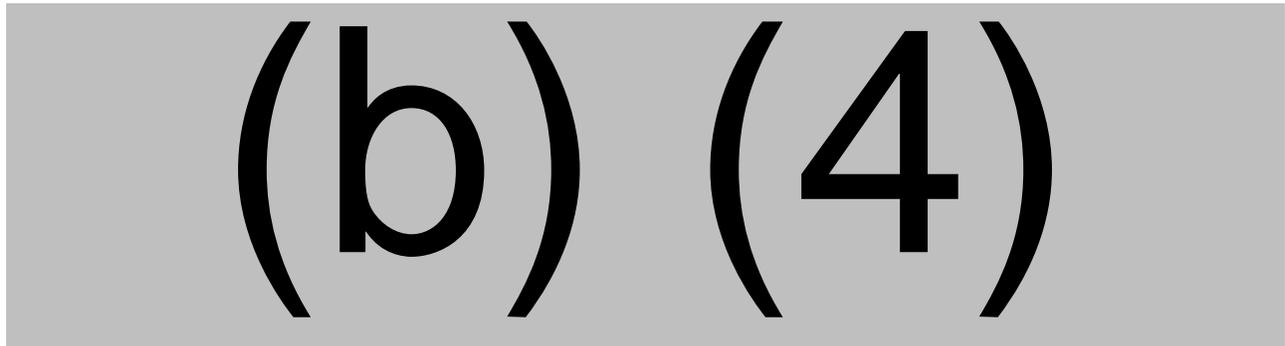
Building/Floor	Area
Building (b) (4) / Floor (b) (4)	<ul style="list-style-type: none"> • QC/ PDE laboratories (NC areas) • QC Classified areas (Grade (b) (4), Grade (b) (4) and Grade (b) (4)) for sterility test • (b) (4) QC/ PDE laboratories • Storage area for QC/PDE • Server Room
Building (b) (4) / Floor (b) (4)	<ul style="list-style-type: none"> • manufacturing classified and not classified areas ((b) (4)) • Medicinal Products storage area • Starting materials storage area • Raw materials internal warehouses
Building (b) (4) / Floor (b) (4)	<ul style="list-style-type: none"> • Raw materials entrance before moving to raw materials warehouse
Building (b) (4) / Floor (b) (4)	<ul style="list-style-type: none"> • Raw material warehouse • GMP Documentation Archive

The manufacturing areas can be subdivided into (b) (4) :

(b) (4)



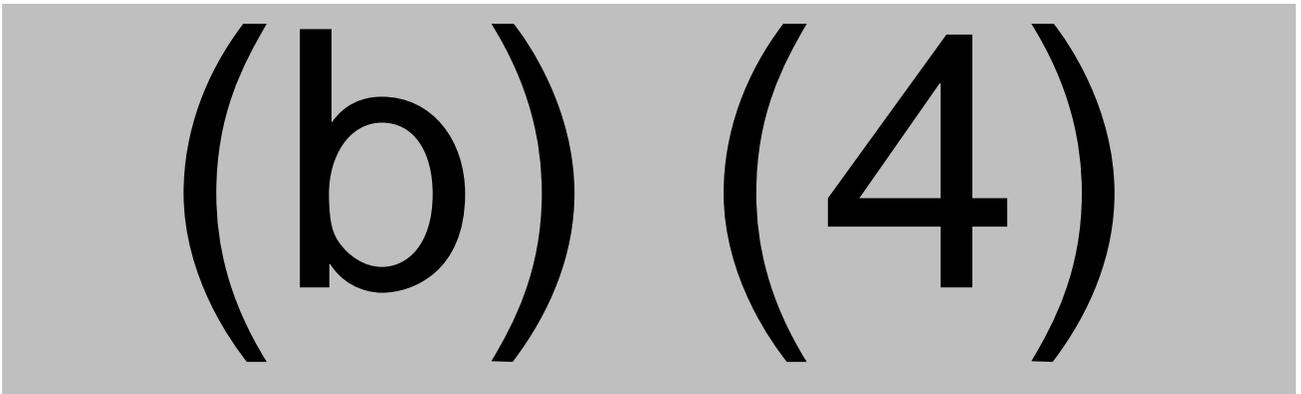
The manufacturing rooms where OTL-200 DS and DP are produced are located in (b) (4) .



*These manufacturing areas are used for the manufacture of OTL-200 DS and DP and for the (b) (4) LV vectors.

The following sections refer to the AGC Biologics facility unless otherwise noted for (b) (4) Bresso buildings specifically:

Manufacturing Areas and Classification



Personnel, Materials, Product and Waste Flows

Flow of personnel from point of entry in the building to the point of work, including activities such as gowning, are optimized to avoid simultaneous presence of “dirty” and “clean” operators. Dedicated personnel airlocks are present to access production areas. Even though the flow of personnel is not unidirectional, the avoidance of simultaneous presence of “dirty” and “clean” operators at any specific location, in accordance with approved procedures, ensures that the risk of personnel-driven cross-contamination is minimized.

Flow of materials/ products and waste are optimized to minimize simultaneous presence of materials, products and waste within the production areas. Materials enter production areas through pass boxes. Before entering classified areas, external wrapping, where applicable, is removed and all materials are externally cleaned/ sanitized. Products are transferred from production rooms through the same pass boxes and corridors used for the transfer of materials. The material and product flows are separated in time in accordance/compliance with specific internal procedures to minimize the risk of contamination.

Raw materials and supplies identification (item number, batch number, expiry date) and status (quarantine, released, rejected) are managed through an Enterprise resource planning (ERP) system and adequate labeling. This allows traceability up to their use in each production area. Waste is transferred from the manufacturing rooms in the common corridors of the manufacturing area through changing rooms separated from materials and products. All the waste is wrapped in bags and decontaminated before exiting the manufacturing rooms in accordance/compliance with specific internal procedures. In addition, a dedicated waste airlock is present in the production area to separate the waste flow from materials/ products flow.

Reviewer’s Assessment: *The facility layout and flow descriptions were reviewed and found acceptable. Facility layout and flows were verified during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to 11/20/2023. No issues were noted.*

Prevention of contamination and cross-contamination

The design of the AGC Biologics facility permits production to take place in areas connected in a logical order corresponding to the sequence of the operations and required level of cleanliness. The arrangement of the working environment and of the equipment and materials is designed to minimize the risk of errors between different products or their components, to avoid cross-contamination of raw materials and manufactured products, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps. All operations are described in standard operating procedures, and only authorized and trained personnel are allowed into manufacturing areas, through a badge reading system.

When a new product is introduced to the AGC Biologics facility, an assessment of the risk presented by the new product is conducted. The assessment is based on control elements already implemented at the facility to avoid any risk of cross-contamination. The facility is designed to ensure that contamination and cross-contamination are prevented with use of separate, classified areas that are serviced by separate air handling units (AHUs). Pressure differentials are designed for containment and protection. Containment strategies in areas used for LVV manufacturing, include the use of (b) (4) in addition to containment and production in LVV manufacturing areas. Additionally, (b) (4) are employed for product protection. Differential pressures are continuously monitored and alarmed to ensure maintenance of the proper room environment.

The air treatment unit is dedicated for each manufacturing room and its associated changing room. This avoids any contamination that could be caused by recirculating air. Specific cleaning/ sanitization procedures have been put in place in case of large spillages on the floor surfaces of the facility and/ or equipment, and specific studies have been performed to evaluate the effect of sanitizers on (b) (4). This has enabled the identification of the correct sanitizing agent to be used at the end of each production run prior to starting a new production run.

The manufacturing operations are conducted in separate and secure areas designed specifically for their respective use. The manufacturing areas are of suitable size for the orderly placement, operation, and maintenance of manufacturing and control equipment and for the orderly flow of personnel and materials. Activities that support the manufacturing process, such as waste decontamination, and material staging are performed in dedicated areas that are physically separated from the manufacturing areas. Segregation of the product manufacturing areas includes the use of production rooms, in which only one batch of product at a time can be manufactured. The personnel and material flows between the manufacturing process areas are segregated.

Additionally, sterilized supporting materials, where needed, are used for production. After completion of each production step, the working areas are cleared and sanitized. The equipment and supporting materials are cleaned/ sanitized according to internal procedures and in compliance with cGMPs. Manufacturing area clearance is performed according to written and approved procedures. Segregation of product is achieved by unique product code and specific lot numbering.

Reviewer's Assessment: *The contamination and cross-contamination control features and procedures are reviewed and found acceptable. Facility cleaning and room changeover procedures were verified during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to 11/20/2023. No issues were identified.*

Facility cleaning and disinfectant effectiveness studies

All items used within the controlled manufacturing areas have been designed specifically for clean room use and maximum cleanability. The materials of construction minimize the generation of particulate matter and are compatible with all cleaning and sanitizing agents used to disinfect the facility. All furniture that is stationary and fixed to the facility have been properly sealed and caulked to vertical and horizontal surfaces to eliminate cracks and crevices and to enhance cleanability.

Internal procedures require sanitizing and disinfecting surfaces, walls, and floors of manufacturing areas to meet cleanroom standards using suitable and validated sanitizing agents and disinfectants. The sanitization is performed using ^{(b) (4)} different sanitizers **(b) (4)**. All disinfection processes are validated demonstrating the disinfectant's ability to reduce surface bioburden including **(b) (4)** strain and common facility flora.

Cleaning/sanitization and disinfection occur according to the following schedule:

^{(b) (4)} [Redacted]

[Redacted]

[Redacted]

[Redacted]

In addition to the cleaning and sanitization procedures described above, specific cleaning and sanitization procedures using a detergent and sporicidal agent are used after an HVAC shutdown.

Reviewer's Assessment: *The disinfectants used at the AGC Biologics S.p.A. facility appear suitable and appropriately qualified. Additionally, overall facility cleaning were verified during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to 11/20/2023 and discussed in the Establishment Inspection Report. No issues were identified.*

HVAC

The heating, ventilation, and air conditioning (HVAC) system in the facility is designed to provide environmentally controlled air suited to meet cGMP requirements. The HVAC system is designed to maintain rooms at predetermined temperatures. Room pressure differentials are established and routinely monitored. Air flow velocity, humidity, pressure and temperature are monitored by independent monitoring systems. Environmental quality is monitored through nonviable particulate matter standards and microbial alert. Appropriate action levels for the manufacturing areas have been established.

The HVAC system that supplies air to the production areas of the (b) (4) building is provided make up unit systems that (b) (4)

[Redacted]

The makeup units supply air to the AHU, dedicated for each manufacturing room and adjacent changing room, that treats (b) (4)

[Redacted]

The HVAC system that supplies that supplies air to the production areas of the Bresso building is provided by (b) (4)

[Redacted]

These make up units supply (b) (4)

[Redacted]

For (b) (4) Bresso buildings, in the Grade (b) (4) and Grade (b) (4) production rooms there are (b) (4) that take air from the Grade (b) (4) Grade (b) (4) room itself, air exhausted by (b) (4) is totally exhausted and does not reenter the room.

Temperature (°C), %RH and differential pressures of production rooms are monitored by a validated BMS. The temperature is maintained between (b) (4), whereas RH% is maintained between (b) (4). Make up systems and AHUs are under emergency electrical power generators while the (b) (4) in which the product could be exposed are under UPS (Uninterruptible Power Supply) in order to ensure the continuity of the (b) (4) operation to allow the closure of the product in case of blackout.

Performance qualification of the HVAC included: verification of particle contamination in “Operating” conditions, and verification of microbiological contamination in “at rest” and “in operation” conditions.

Reviewer’s Assessment: HVAC design and qualification was reviewed and found acceptable. The HVAC requalification was verified during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to 11/20/2023. Details are noted in the EIR. No issues were identified.

Environmental Monitoring

The production areas are periodically monitored in terms of non-viable particles and viable particles through active air monitoring, passive air monitoring (using (b) (4)), and surfaces ((b) (4)). Additionally, monitoring of personnel working in sterile areas is performed. All sampling areas have been selected based on worst case locations and covered under the Environmental Monitoring Qualification Program (EMPQ).

Viable particulate monitoring limits are described below:

(b) (4)

(b) (4)

Any excursion which exceeds the action level is formally investigated and an identification of microorganisms for Grade (b) (4) and Grade (b) (4) production rooms is made to establish preventive actions. The microbiological data collected are trended in accordance with specific approved procedures. In addition to action levels, alert levels have also been defined according to historical monitoring data. The necessity to review these limits is (b) (4) evaluated according to (b) (4) trending of the data.

For Grade (b) (4), Grade (b) (4) and Grade (b) (4) areas molds are also routinely monitored and assessed and trended every (b) (4) using (b) (4) for passive air, active air and surfaces.

In case molds are detected, the following actions are implemented:

(b) (4)

For all classified areas non-viable particles monitoring is performed by (b) (4) samples as part of the qualification of the facility air system and is carried out routinely in the different classified areas. For the Grade (b) (4) areas ((b) (4)) and Grade (b) (4) surrounding the continuous non-viable particles monitoring is performed. The action levels are presented below and are aligned with (b) (4)

(b) (4)

- Grade (b) (4) action limit: (b) (4)
- Grade (b) (4) action limit: (b) (4)
- Grade (b) (4) - : (b) (4)

Reviewer’s Assessment: The information provided for the EM program and routine monitoring appears acceptable. Additionally, the overall EM was evaluated during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to 11/20/2023 and discussed in the EIR. No issues were identified.

Equipment Qualification

Qualification activities for major equipment used in AGC Biologics Milan facility for (b) (4), OTL-200 DS and DP are noted below:

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

(b) (4)

Reviewer's Assessment: Major equipment qualifications were verified during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to

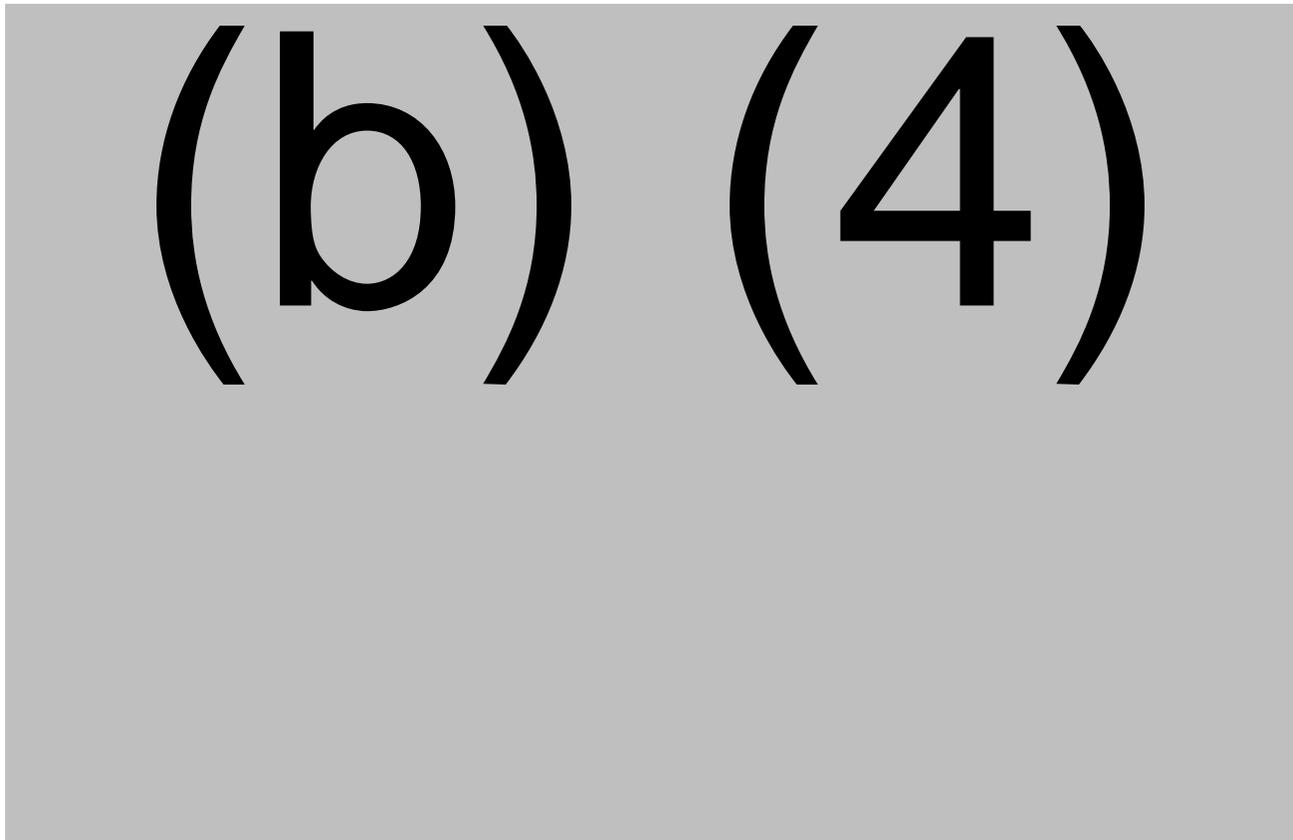
11/20/2023 and are described in the Establishment Inspection Report. The inspection was classified as VAI.

Equipment Cleaning and Sanitization

All product contact equipment is single use, disposable, with the exception of the (b) (4) which are product dedicated. (b) (4) are single-use and discarded after each production batch. The equipment is periodically cleaned/sanitized as required by cleaning/sanitization internal procedures. The (b) (4) equipment is sanitized (b) (4).

For all equipment, cleaning/sanitization activities are performed in accordance with specific approved procedures, including procedures for cleaning in case of spillage. The cleaning/sanitization activities are recorded in specific cleaning logbooks.

A summary of the cleaning/sanitization procedure for (b) (4) written in accordance with equipment supplier recommendations, is presented the table below:



The cleaning/sanitization procedure has been validated to demonstrate its effectiveness in removing (b) (4) and maintain a controlled microbial level. The (b) (4)

and the instrument are sanitized (b) (4) and clean holding times have been validated.

Three consecutive cleaning validation runs were performed on the (b) (4). The runs were concurrent with the production of PPQ batches (b) (4). Acceptance criteria for samples collected following (b) (4) were set based on the (b) (4).

All acceptance criteria were met.

In addition, changes to the cleaning process were introduced in 2020. The changes included (b) (4). The changes resulted in a complementary validation study being carried out. The study incorporated (b) (4) different processes run across (b) (4).

All samples met acceptance criteria demonstrating the efficacy of the cleaning process.

The potential for cross-contamination from incidental product contact surface areas and product contact areas have been assessed. Incidental product contact surface areas are those that may not be directly in contact with the product, but which can contribute to the risk of cross-contamination. For indirect or incidental product contact equipment, cleaning verification studies have been performed for (b) (4) which have been documented in specific protocols and reports.

The scope of these verification studies was to evaluate the removal of (b) (4) from surfaces in case of product spillage. The verification studies used sanitizing agents employed for cleaning/ sanitization of equipment/ manufacturing areas. For “non-product contact” equipment, the risk of cross-contamination is negligible, and no additional evaluations, beyond the risk assessment, have been conducted. In case of spillage, dedicated internal cleaning procedures are followed.

Reviewer’s Assessment: *Cleaning validation, disinfectants utilized, and their efficacy were verified during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to 11/20/2023 and are described in the Establishment Inspection Report. The inspection was classified as VAI. The changes introduced in 2020 were intended to address the deviation associated with (b) (4) contamination in the (b) (4). The complementary validation study further supports the adequacy of the changes implemented.*

Critical Utilities

Critical utility systems used in the AGC Biologics Milan facility for (b) (4) OTL 200 (b) (4) DP manufacturing are listed in the table below.

Critical Utility Systems

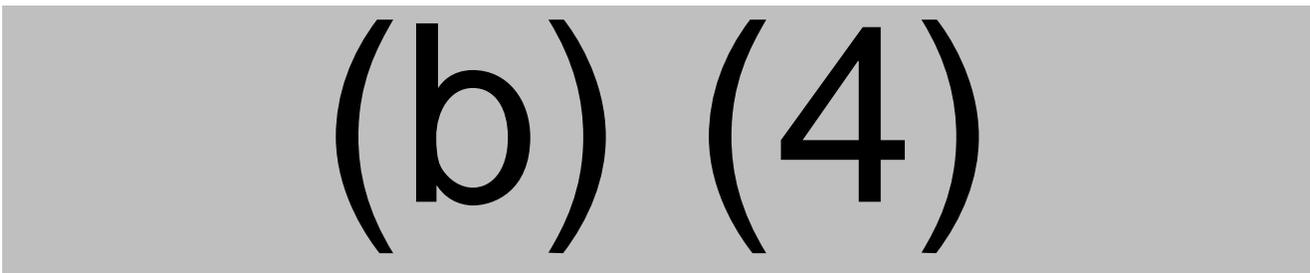
Type of Utility	Description	Point of Use
Gas	(b) (4)	(b) (4)
Liquids	Softened Water (SW) (Internal limits)	
Liquids	Purified Water (b) (4)	
Liquids	Clean steam (b) (4)	
Liquids	Liquid Nitrogen (b) (4)	

To prevent any type of contamination, the utilities listed above are qualified and periodically monitored according to internal procedures and EU and US Guidelines. The gas (b) (4) is (b) (4) located at the point of use that are (b) (4) tested and replaced (b) (4). (b) (4) analysis are performed on an (b) (4) basis. The softened water (SW) is periodically monitored for (b) (4) analysis in accordance with internal procedures. The clean steam is periodically monitored for (b) (4) analysis in accordance with internal procedures.

Reviewer’s Assessment: *The WFI used in manufacturing is purchased. The qualification and monitoring of utilities appear acceptable and were verified during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to 11/20/2023. No issues were identified.*

Computer Systems

The major GMP critical computerized systems used in the AGC Biologics Milan facility per building are listed in the tables below:



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

(b) (4)

GMP critical computerized systems involved in the manufacturing, testing and supervision activities are validated and maintained in compliance with the cGMP requirements throughout their life cycle. The validation of computerized systems is a documented process to ensure that a computerized system does exactly what it was designed to do in a consistent and reproducible way (suitability to use), ensuring the integrity and security of data processing, product quality, and complying with GMP applicable regulations. The validation process begins with validation planning, system requirements definition, testing and verification activities, and validation reporting. The system lifecycle then enters the operational phase and continues until system retirement and retention of system data based on regulatory rules.

Reviewer's Assessment: *The information on the computer systems provided appears acceptable. Computer systems were evaluated during Pre-License Inspection at AGC Biologics S.p.A, Milan, Italy conducted from 11/08/2023 to 11/20/2023. No issues were identified.*