

**CBER DMPQ CMC/Facility BLA Review Memorandum**

**BLA STN 125798/0**

**revakinagene taroretcel-lwey, (NT-501); ENCELTO**

**Miriam Ngundi, Consumer Safety Officer, OCBQ/DMPQ/MRB1**

**1. BLA#: STN 125798/0**

**2. APPLICANT NAME AND LICENSE NUMBER**

Neurotech Pharmaceuticals, Inc.; License No: 2321

**3. PRODUCT NAME/PRODUCT TYPE**

Non-proprietary/proper/USAN: revakinagene taroretcel-lwey (NT-501)

Proprietary name: ENCELTO

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

- a. Pharmacological category: Allogeneic encapsulated cell-based gene therapy product
- b. Dose form: Biologic/device combination product comprised of a semipermeable capsule that has been loaded with ciliary neurotrophic growth factor (CNTF)-secreting NTC-201-6A cells
- c. Strength/Potency: > 200,000 allogeneic retinal pigment epithelial cells expressing hCNTF per implant
- d. Route of administration: surgical implantation into the vitreous cavity
- e. Indication(s): Treatment of adults with idiopathic macular telangiectasia type 2 (MacTel)

**5. MAJOR MILESTONES**

Filing action date: June 17, 2024

Facility inspection: July 22 – 26, 2024

Mid-cycle meeting with Neurotech: August 20, 2024

Late-cycle meeting with Neurotech: October 07, 2024

Designation of major amendment: October 31, 2024

PDUFA action date: March 18, 2025

**6. DMPQ CMC/FACILITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Miriam Ngundi, OCBQ/DMPQ/MRB1	3.2.S – Drug substance, 3.2.P 3 – Combination drug product, 3.2.A.1 – Facilities and equipment, and 3.2.R – Regional information (Device constituent)
Massoud Motamed, OCBQ/DMPQ/MRB1	Remote Regulatory Assessment, 704(a)(4) Records Request – (b) (4)

**7. SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
04/18/2024	STN 125798/0	Original submission / Reviewed

Date Received	Submission	Comments/ Status
05/17/2024	Amendment STN 125798/0.3 Response to information request (IR) dated 05/10/2024	Information to prepare for pre-license inspection / Reviewed
05/24/2024	Amendment STN 125798/0.5 Response to information request (IR) dated 05/13/2024	(b) (4) adhesive sterility test validation / Reviewed
06/14/2024	Amendment STN 125798/0.10	Updated stability data / Reviewed
08/06/2024	Amendment STN 125798/0.20 Response to IR dated 07/23/2024	Update on endotoxin testing site / Reviewed
08/16/2024	Amendment STN 125798/0.24 Response to Form FDA 483	PLI - Response to Form FDA 483 observations issued on 07/26/2024 / Reviewed
08/30/2024	Amendment STN 125798/0.31 Response to Form FDA 483 follow-up #1	PLI - Response to Form FDA 483 observations issued on 07/26/2024 / Reviewed
09/18/2024	Amendment STN 125798/0.36 Response to IR dated 09/04/2024	Process validation, media fill studies / Reviewed
09/25/2024	Amendment STN 125798/0.41 Response to IR dated 09/11/2024	Container closure and container closure integrity testing / Reviewed
09/26/2024	Amendment STN 125798/0.42 Response to IR dated 09/06/2024	Records Request (704(a)(4)) / Reviewed
09/30/2024	Amendment STN 125798/0.43 Response to Form FDA 483 follow-up #2	PLI - Response to Form FDA 483 observations issued on 07/26/2024 / Reviewed
10/07/2024	Amendment STN 125798/0.45 Responses to the substantive issues in Late Cycle Meeting agenda dated 09/27/2024	Substantive CMC issues for Late Cycle Meeting / Reviewed
10/08/2024	Amendment STN 125798/0.46 Response to IR dated 09/23/2024	Response to RAI for response to Form FDA 483 / Reviewed
10/16/2024	Amendment STN 125798/0.49 Response to IR dated 10/01/2024	Container closure system (CCS), facilities and equipment qualification / Reviewed – Major amendment
10/17/2024	Amendment STN 125798/0.50 Neurotech's questions post informal meeting held 10/10/2024	Questions on media fill study, container closure integrity test (CCIT), and CCS / Reviewed

Date Received	Submission	Comments/ Status
10/23/2024	Amendment STN 125798/0.53 Response to IR dated 10/09/2024	Media fill studies, CCIT, and (b) (4) adhesive / Reviewed
10/25/2024	Amendment STN 125798/0.56 Follow-up to response to IR dated 09/23/2024	Response to RAI for response to Form FDA 483 / Reviewed
10/30/2024	Amendment STN 125798/0.60 Response to IR dated 10/09/2024	CCIT validation protocol / Reviewed
11/15/2024	Amendment STN 125798/0.64 Follow-up to response to IR dated 10/01/2024	Shipping validation/ Reviewed
11/25/2024	Amendment STN 125798/0.67 Response to IR dated 11/08/2024	EMPQ, media fill studies, CCIT, disinfectant efficacy, equipment / Reviewed
12/06/2024	Amendment STN 125798/0.69 Response to Form FDA 483 follow-up	PLI - Response to Form FDA 483 observations issued on 07/26/2024 / Reviewed
12/16/2024	Amendment STN 125798/0.71 Response to IR dated 11/22/2024	Records Request (704(a)(4)) / Reviewed
12/30/2024	Amendment STN 125798/0.72 Response to IR dated 12/05/2024	EMPQ, (b) (4) validation, disinfectant efficacy / Reviewed
12/30/2024	Amendment STN 125798/0.73 Follow up to response to IR dated 11/08/2024	CCIT / Reviewed
01/10/2025	Amendment STN 125798/0.74 Response to IR dated 10/09/2024	Media fill study report / Reviewed
01/15/2025	Amendment STN 125798/0.78 Response to IR dated 11/08/2024	(b) (4) validation study report / Reviewed
01/31/2025	Amendment STN 125798/0.80 Response to IR dated 01/24/2025	(b) (4), equipment, shipping / Reviewed
01/31/2025	Amendment STN 125798/0.81 Response to IR dated 10/09/2024	CCIT validation report / Reviewed
02/04/2025	Amendment STN 125798/0.82 Response to IR dated 01/31/2025	(b) (4) media fills / Reviewed
02/11/2025	Amendment STN 125798/0.83 Response to IRs dated 10/01/2024 and 11/08/2024	Disinfectant efficacy study interim report / Reviewed
02/11/2025	Amendment STN 125798/0.84 Response to IR dated 02/07/2025	Reporting category for CCS supplier / Reviewed
02/12/2025	Amendment STN 125798/0.85 Response to IR dated 02/10/2025	(b) (4) bioburden / Reviewed

Date Received	Submission	Comments/ Status
02/14/2025	Amendment STN 125798/0.89 Response to Observation Letter dated 01/27/2025	Response to (704(a)(4)) Observation Letter / Reviewed
02/18/2025	Amendment STN 125798/0.91 Response to IR dated 02/14/2025	Postmarketing Commitments / Reviewed
02/21/2025	Amendment STN 125798/0.92 Response to IR dated 02/19/2025	Postmarketing Commitments / Reviewed
02/27/2025	Amendment STN 125798/0.94 Response to IR dated 02/25/2025	Postmarketing Commitments / Reviewed

## 8. REVIEWER SUMMARY AND RECOMMENDATION

### A. EXECUTIVE SUMMARY

Neurotech Pharmaceuticals, Inc (referred to as Neurotech or the applicant) submitted a Biologics License Application (BLA) STN 125798/0 on April 18, 2024 to support the licensure of revakinagene taroretcel-lwey (NT-501), ENCELTO, an implant containing allogeneic retinal pigment epithelial cells (NTC-201-6A) expressing human ciliary neurotrophic factor (hCNTF). ENCELTO is a biologic/device combination product comprised of a semipermeable capsule loaded with > 200,000 NTC-201-6A cells. ENCELTO is surgical implantation by intravitreal insertion (via a pars plana sclerotomy) and is indicated for the treatment of adults with macular telangiectasia (MacTel) type 2. On June 17, 2024, FDA issued a filing notification to the applicant that the BLA received a Priority Review designation.

ENCELTO is manufactured at Neurotech Pharmaceuticals, Inc. located in Cumberland, RI. The manufacture of ENCELTO is a continuous process, starting from the initiation of (b) (4) to manufacture (b) (4) (b) (4) cell-loaded semipermeable capsule, which constitutes the manufacture of the biologic/device combination product (ENCELTO). The semipermeable capsule (referred to as NT-501 pre-assembled capsule (NT-501 PAC)) – the device constituent of ENCELTO) is manufactured (i.e., assembly of the PAC with its accessories including anchor loop, (b) (4) and gripper) at (b) (4). The NT-501 PAC is then sterilized at (b) (4). This review memo provides the summaries and assessments of 1) ENCELTO manufacturing process including product quality attributes with emphasis on microbial controls and 2) facility and equipment including qualification of utilities and manufacturing equipment, cross-contamination controls, qualification and maintenance of classified environments, cleaning/sterilization and maintenance of equipment, and sterilization of NT-501 PAC and product package components.

The Office of Compliance and Biologics Quality, Division of Manufacturing and Product Quality (OCBQ/DMPQ) and the Office of Therapeutic Products (OTP) conducted a pre-license inspection (PLI) of the Neurotech Pharmaceuticals, Inc. facility (Cumberland, RI, FEI # 3012545799). A three-item Form FDA 483 Inspectional Observations was issued

at the conclusion of the Neurotech PLI, and the PLI was classified as Voluntary Action Indicated (VAI).

A Remote Regulatory Assessment (RRA) was conducted to request records in lieu of inspection of the (b) (4) under section 704(a)(4) of the FD&C Act. Remote Regulatory Assessment Observations (RRAO) identified during the manufacturing site's RRA were communicated to the firm in an RRAO letter. The RRA was classified as Remote – Voluntary Action Indicated (rVAI).

In addition to the PLI and RRA, facility inspections were waived following an evaluation of the inspection compliance histories of the device constituent sterilization and DP release testing facilities:

- (b) (4)

Note, the inspection waiver for these facilities is documented in a separate inspection waiver memo dated November 24, 2024.

Based on the information submitted to BLA 125798/0, PLI, RRA, and inspectional compliance history evaluations, the facilities, equipment, and microbial controls appear acceptable for the licensure of ENCELTO, and approval is recommended.

## **B. RECOMMENDATION**

### **I. APPROVAL**

Based on the information provided in the original application and amendments, DMPQ recommends the approval of revakinagene taroretcel-lwey (NT-501), ENCELTO, which is manufactured at Neurotech Pharmaceuticals, Inc. 900 Highland Corporate Dr., Building 1, Suite 101, Cumberland, RI 02864, with the following Postmarketing Commitments (PMCs):

1. Neurotech commits to perform a (b) (4) validation study that includes (b) (4). The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by July 31, 2025.
2. Neurotech commits to perform (b) (4). The final report will be submitted as a "Postmarketing Commitment - Final Study Report" by July 31, 2025.

**II. SIGNATURE BLOCK**

<b>Reviewer/Title/Affiliation</b>	<b>Concurrence</b>	<b>Signature and Date</b>
Miriam Ngundi, CSO, OCBQ/DMPQ/MRB1	Concur	
Kathleen Jones, Branch Chief, OCBQ/DMPQ/MRB1	Concur	
Carolyn Renshaw, Director, OCBQ/DMPQ	Concur	


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### 3.2.S DRUG SUBSTANCE

(b) (4)



#### 3.2.S.2 Manufacture


##### 3.2.S.2.1 Manufacturer(s)

ENCELTO DS is manufactured at Neurotech Pharmaceuticals, Inc., 900 Highland Corporate Dr., Building 1, Suite 101, Cumberland, RI 02864.

*Reviewer's comment:* See section 3.2.A.1 for a complete list of the manufacturing activities performed at the Neurotech facility as well as other facilities used to manufacture (b) (4) and storage and testing) the DS.


##### 3.2.S.2.2 Description of Manufacturing Process

(b) (4)





(b) (4)



### **3.2.P DRUG PRODUCT (COMBINATION PRODUCT)**

#### **3.2.P.1 Description and Composition of the Combination Product**

ENCELTO is a sterile, non-pyrogenic biologic/device combination product comprising of a pre-assembled/semipermeable capsule (NT-501 PAC, the device constituent) loaded with formulated NTC-201-6A cells (b) (4) and sealed with methacrylate adhesive (b) (4). ENCELTO is surgically implanted by intravitreal insertion (via a pars plana sclerotomy), and the encapsulated NTC-201-6A cells secrete hCNTF, which is indicated for the treatment of idiopathic macular telangiectasia (MacTel) type 2. The ENCELTO dosage form is one implant containing 200,000 – 440,000 NTC-201-6A cells. The active region membrane component of the capsule is approximately (b) (4) mm long, with an internal diameter of approximately 0.87 mm, and a wall thickness of approximately (b) (4) mm.


The NT-501 PAC (device constituent) consists of a titanium anchor loop (fixation loop) for PAC handling as well as polyethylene terephthalate (PET) scaffolding within semipermeable hollow fiber membrane (HFM) for cell support. (b) (4) is used for sealing the NT-501 PAC ends after cell loading. ENCELTO is approximately 6.5 mm long with an external diameter of approximately (b) (4) mm.

The ENCELTO CCS consists of 1) an inner container, which is a two-compartment polycarbonate container. The lower compartment containing ENCELTO suspended in Endo-SFM (hold media) is sealed from the upper dry compartment by a Luer lock cap that supports the titanium clip (gripper) holding the product. The upper compartment is sealed with a polymer-foil composite lid film. 2) an outer polycarbonate container, which holds the inner container and is sealed with a polymer-foil composite lid. The outer container is considered to be the primary packaging / sterile barrier.

#### **3.2.P.2.3 Manufacturing Process Development**





##### **Sterile Filtered (b) (4)**

(b) (4)






(b) (4)



### 3.2.P.2.5 Microbiological Attributes

The microbial controls during the manufacture of sterile ENCELTO include manipulations performed under aseptic conditions using sterile materials and components as well as microbiological testing for IPC, during product lot release, and to support the stability program. The acceptance criteria for IPC samples as well as the ENCELTO lot release and stability include sterility (no growth) and bacterial endotoxins (b) (4) /ENCLETO unit and (b) (4) hold media).

Neurotech claimed that based on a study performed to support aseptic processing (i.e., Study R0276, see section 3.2.P.3.5 Process Validation and/or Evaluation for details), Endo-SFM (hold media) (b) (4)



under normal ENCELTO shelf-life storage conditions. According to the applicant, any microbial contamination present in ENCELTO may be detected by the sterility testing at lot release, because 100% visual inspection is performed during lot

disposition and the product is stored in growth promoting hold media. Therefore, Neurotech proposed to (b) (4). In amendment STN 125798/0.82, Neurotech confirmed it would continue to perform (b) (4) media fills post approval. Additionally, the applicant updated Section 3.2.P.3.5 and removed the reference to (b) (4) aseptic process simulation post approval.

*Reviewer's comment:* The information provided appears acceptable. The manufacture of ENCELTO is conducted in areas that are monitored to meet the requirements of ISO (b) (4) within ISO (b) (4) environments, and incoming materials and components are evaluated to meet sterile properties. The product release specifications also meet sterility criterion of no growth and low risk endotoxin level (b) (4). Testing of the CCS and validation of the container closure integrity test (CCIT) (b) (4) method are documented under sections 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures, and the results appear to indicate that the CCS is acceptable to provide a sterile barrier for ENCELTO.

The study performed to support the ability of Endo-SFM (hold media) to (b) (4). However, the study does not support the detection of (b) (4). Therefore, I assessed that visual inspection of ENCELTO during lot disposition and in storage should not be applied as a sole form of microbial control for ENCELTO to (b) (4). This was communicated to Neurotech, and amendment STN 125798/0.82, Neurotech agreed to continue to perform (b) (4) media fills.

### 3.2.P.3 Manufacture

#### 3.2.P.3.1 Manufacturer(s)


ENCELTO is manufactured at Neurotech Pharmaceuticals, Inc., 900 Highland Corporate Dr., Building 1, Suite 101, Cumberland, RI 02864.

*Reviewer's comment:* See section 3.2.A.1 for a complete list of the manufacturing activities performed at the Neurotech facility as well as other facilities used to manufacture (i.e., manufacture and sterilization of PAC, testing, and storage) the combination product.



#### 3.2.P.3.3 Description of Manufacturing Process

ENCELTO is manufactured by (b) (4) using a semi-automated manufacturing system. The manufacture of ENCELTO is an open process performed under an ISO (b) (4) within an ISO (b) (4) environment (b) (4) suite). The manufacturing process consists of the following steps, all performed continuously inside the (b) (4) (except labeling and storage):

- (b) (4)

- (b) (4)
- 

In amendment STN 125798/0.36, Neurotech clarified that visual inspection (100%) of ENCELTO is performed for risk mitigation purposes (not a ENCELTO lot release test) during lot disposition. The parameters assessed during visual inspection include:

- (b) (4)
- 
- 

. In amendment STN 125798/0.53, Neurotech revised the sampling plan for sterility testing during the commercial manufacture of ENCELTO.

In amendment STN 125798/0.67, Neurotech revised the sterility sampling plan again (b) (4)

The firm stated that the corresponding procedures were updated to align with the sampling plan.

There is no reprocessing involved in the manufacture of ENCELTO combination product.

*Reviewer's comment: Neurotech provided a clear stepwise description used to manufacture ENCELTO combination product. The applicant provided the flow chart for the manufacturing process (Table 1) as well as schematic diagrams (Figures 1 – 10) The information provided to describe the manufacturing process appears acceptable. The revised sampling plan for the routine sterility testing of the sterile ENCELTO combination product as provided in amendment STN 125798/0.67 appears acceptable and aligned with the principles of sampling of an aseptic process for sterility testing.*

### 3.2.P.3.4 Controls of Critical Steps and Intermediates

The critical step in the manufacture of ENCELTO are the (b) (4)

. The acceptance criteria are:

- (b) (4)

Neurotech provided the IPC results for the ENCELTO PPQ lots (b) (4) which met the above acceptance criteria.

(b) (4)



- (b) (4)

(b) (4) summarized in section 3.2.P.2.3  
Manufacturing Process Development.

There are no intermediates in the manufacture of NT-501 combination product.

*Reviewer's comment: The information provided appears acceptable. The sterility of the (b) (4) adhesive is tested per (b) (4) with an acceptance criterion of no growth. Additionally, Neurotech has established a sterile (b) (4) adhesive of (b) (4) (please see Section 3.2.P.2.3). The data appear to indicate an appropriate control strategy is implemented to assure product quality and sterility and process consistency.*



### 3.2.P.3.5 Process Validation and/or Evaluation

#### Process Performance Qualification (PPQ)

Neurotech provided a summary of a process validation study performed using (b) (4) ENCELTO PPQ lots described in Table 1 including associated batch record process and batch record associated lot number (b) (4) combination product). The (b) (4) ENCELTO batches (b) (4) met the CPP acceptance criteria (Table 4) including the (b) (4) seal of the inner and outer containers (i.e., (b) (4)). The (b) (4) lots were labeled as lots (b) (4) (manufactured on (b) (4)) (manufactured on (b) (4)) (manufactured on (b) (4)) respectively.

(b) (4)

(b) (4)




*Reviewer's comment:* The information provided for the process validation appears acceptable. The data to support the process validation met the predefined acceptance criteria. The applicant's conclusion that the ISO (b) (4) environments maintained a state of control during operations and the action taken to address the deviations appear acceptable.

**Aseptic Process Simulation (APS) of ENCELTO Manufacturing Process**

The manufacture of ENCELTO is performed using (b) (4)



In amendment STN 125798/0.36, Neurotech stated that the following manufacturing steps are simulated during media fill studies:

- (b) (4)
- 



- (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **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)**

Neurotech provided the proposed lot release specifications for ENCELTO in Table 1., which included the following:

- Sterility (b) (4) [REDACTED] No growth (both ENCELTO unit and hold medium)

- Endotoxin (b) (4) /ENCELTO unit; (b) (4) of hold medium

Container closure integrity is not assessed as a lot release test.

*Reviewer's comment: The microbial release testing is performed according to (b) (4) methods. Review of the other release specifications is deferred to OTP, and review of the validations if the microbial release test methods is deferred to DBSQC.*

### 3.2.P.5.4 Batch Analyses

Neurotech provided the batch analyses of (b) (4) ENCELTO PPQ batches. (b) (4) of the manufactured batches had (b) (4) product units in each, and the (b) (4) batch consisted of (b) (4) units. The results for all the batches met the acceptance criteria for sterility (b) (4) no growth for product and hold medium) and bacterial endotoxin (b) (4) /ELCETO product and (b) (4) for hold medium).

*Reviewer's comment: The information provided appears acceptable. All tests results for sterility and bacterial endotoxin met the release acceptance criteria for all batches. The data appear to indicate that a sterile ENCELTO may be consistently manufactured at the Neurotech Pharmaceuticals, Inc. facility.*

### 3.2.P.7 Container Closure System

#### Description of container closure system and packaging

The CCS of ENCELTO consist of an inner container and an outer container (primary packaging). Neurotech stated that the outer container provides sterile protection of ENCELTO during shelf life, shipping, and surgical preparation.

The inner container consists of the following components:

- Polycarbonate blue tinted container with lower and upper compartments supplied by (b) (4)
- Luer lock cap made up of a polycarbonate locking ring and polypropylene baffle cap. The luer lock cap is supplied by (b) (4)
- Lid film. The lid is a foil/film composite consisting of a foil with vinyl base (b) (4) layer, adhesive, (b) (4) polyethylene terephthalate (PET), and a universal sealant. The lid is supplied by (b) (4)

Neurotech stated that an additional supplier for the polycarbonate container and luer lock cap will be added after the BLA's approval, and the change will be submitted to the Agency as a CBE-30. In amendment STN 125798/0.80, Neurotech committed to submit the introduction of an additional supplier for the inner container and luer lock cap as a PAS following approval of the BLA. In amendment STN 125798/0.84, Section 3.2.P.7 was updated to include the proposed reporting category as a PAS.

The lower compartment of the inner container is filled with Endo-SFM (the maintenance hold medium) into which ENCELTO is suspended. The product is secured to the luer

lock cap using a titanium clip (gripper). The luer lock cap seals the lower compartment. The upper compartment remains dry and allows access to the locking polypropylene luer lock cap.

The outer container (primary packaging) consists of the following components:

- Polyethylene terephthalate glycol blue tint base supplied by (b) (4).
- Lid film. The lid is a foil/film composite consisting of a foil with vinyl base (b) (4) layer, adhesive, (b) (4) PET, and a universal sealant. The lid is supplied by (b) (4).

The components of the inner and outer containers are received non-sterile from the supplier with a CoC. The components are released through Neurotech's Quality Material Management program prior to further packaging for shipment for (b) (4) sterilization at (b) (4). The sterilized components are shipped back to Neurotech accompanied by (b) (4) which indicates the sterilization dose applied for each batch. The (b) (4) details of the dose used and dose mapping of the (b) (4) packaging. Dose auditing at (b) (4) is performed (b) (4), which includes bioburden test on the non-sterile packaging, dose mapping, and sterility testing after sterilization.

Neurotech provided the dimensions of all components of the inner and outer containers as well as examples of the CoC and (b) (4) for each component.

In amendment STN 125798/0.50, Neurotech proposed to revise Section 3.2.P.7 of the BLA to provide clarity on the container closure system. Neurotech stated that the revision presents the ENCELTO primary CCS as the outer container (containing the inner container, luer lock, ENCELTO implant, and ENDO-SFM media) that is hermetically sealed. The applicant defined the secondary CCS as the "(b) (4) Corepack" used for product shipment from the distribution center to surgical site (end user) (additional details below).

In amendment STN 125798/0.53, Section 3.2.P.7, Neurotech described the secondary packaging used during product shipment. At the Neurotech facility, ENCELTO in the primary CCS is placed into a (b) (4) which is design to securely hold up to (b) (4) ENCELTO units in (b) (4) spaces. (b) (4)

(b) (4). ENCELTO is shipped from the distributor to surgical site (end user) per a product order. The shipping pack out at the distribution center includes (1) placement of (b) (4) ENCELTO unit(s) and a temperature recorder into a (b) (4) with its contents and documentation (prescribing information, instructions for use, medium pH color guide, and inspection checklist) into the transport carton (referred to as the (b) (4) Corepack"). Neurotech refers the (b) (4) Corepack and its contents as the (b) (4) Corepack". (3) labeling of the (b) (4) Corepack (i.e., carton label) and (4) placement of the (b) (4) Corepack

into a (b) (4) shipper box with (b) (4) [REDACTED]. Neurotech refers to the complete shipping packaging as the “NT-501 Shipping System”. Neurotech provided the schematic diagrams for the transport packaging of ENCELTO.

In amendment STN 125798/0.50, Neurotech explained that the outer container maintains the sterile barrier for the inner container which must be sterile when transferred to the sterile surgical field. Neurotech explained that the inner tray seal is not designed nor intended to provide a sterile barrier but is only in place as an additional ‘dust cover’ for presentation to the sterile field, and therefore, the inner container foil lid film must be hermetically sealed to maintain a redundant, sterile barrier. In FDA’s response (sent to Neurotech on October 18, 2024) to Neurotech’s questions posed during a teleconference held on October 10, 2024 and submitted as amendment STN 125798/0.50, CBER concurred with Neurotech that a validation study of the inner container tray sealing process does not need to be performed.

In amendment STN 125798/0.53, Neurotech revised Section 3.2.P.7 (narratives and figures) to clarify that the primary ENCELTO CCS consists of the outer container, which contains the inner container with a luer lock separating the two compartments of the inner container. Neurotech stated that the outer container is hermetically sealed and is the only sterile barrier for ENCELTO. Neurotech explained that a label is applied to the outer container (primary packaging) during the manufacture of ENCELTO at Neurotech, and another label is applied to the (b) (4) [REDACTED] Corepack (secondary packaging) at the distributor prior to shipment to the surgical site. The applicant provided the details of the packaging operations (at Neurotech before shipment to distributor as well as packaging at the distributor before shipment to surgical site).

### **Container closure integrity**

The following information on the validation of the outer container (primary package) seal’s integrity was provided in Sections 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.

Container closure integrity testing (CCIT) is performed to support the container closure system and as part of the stability program to support the shelf life of ENCELTO. Neurotech ships ENCELTO to a third party vendor ((b) (4) [REDACTED]) for CCIT for the stability program. The original submission indicated that CCIT is performed using the (b) (4) [REDACTED] method (per (b) (4) [REDACTED] testing). Neurotech stated that the test method validation results were summarized in document OQ-Q2304085. However, OQ-Q2304085 documented the validation of the inner and outer containers sealing process, which was executed (b) (4) [REDACTED] (please see Section 3.2.P.2.3).

Note: The (b) (4) [REDACTED] method states that it is not necessarily applicable to combination products. In amendment STN 125798/0.41, Neurotech explained its rationale for the using the (b) (4) [REDACTED] method, based on the comprehensive and redundant tests that ensure CCI and sterility assurance, which included the following:

- Lot release sterility (b) (4) [REDACTED] testing

- Visual inspection at lot release – leak to outer container, media color change and clarity
- CCIT during stability program
- Visual inspection at the surgical center using the method described in the ENCELTO instructions for use and validated human factors study

Neurotech stated that the above comprehensive and validated testing approach justifies replacing (b) (4) with the (b) (4) testing methodology that includes the above tests.

In amendments STNs 125798/0.50 and 125798/0.53, Neurotech proposed to develop and validate a CCIT method based on (b) (4). The validated method would replace (b) (4) for CCIT for stability testing of ENCELTO. Neurotech proposed to use the validated CCIT method on the ENCELTO primary packaging (identified as the outer container), which maintains the sterile barrier. In FDA's response (sent to Neurotech on October 18, 2024) to Neurotech's questions posed during the teleconference held on October 10, 2024 and submitted as amendment STN 125798/0.50, CBER concurred with Neurotech's proposal to perform an appropriate and validated CCIT on the outer container, which the applicant defined as the sterile barrier. In amendment STN 125798/0.53, Neurotech stated that the (b) (4) is a (b) (4) method, which is considered to be validated. Therefore, Neurotech conducted a verification study to ensure the method's suitability for detecting leaks in the ENCELTO primary CCS.

In amendments STN 125798/0.60 and STN 125798/0.73, Neurotech provided the CCIT method validation protocol and transportation study protocol.

In amendments STN 125798/0.67, Neurotech clarified that the development and optimization of the (b) (4) method for the CCIT of ENCELTO will be performed by (b) (4). The Neurotech facility and (b) (4) will then co-validate the method. The Neurotech facility would then use the validated method to perform the CCIT of ENCELTO CCS for shipping validation and the stability program. Additionally, the firm committed to update Section 3.2.P.3.1 upon completion of the method validation.

In amendment STN 125798/0.81, Neurotech provided the validation report (RCD-000164.01) for CCIT (b) (4) method (b) (4). The validation was executed at the Neurotech facility using validation protocol RCD-000159. Neurotech explained that all test articles were manufactured according to Neurotech's batch records for ENCELTO (b) (4), except for the use of (b) (4) (i.e., in the place of Endo-SFM) in the inner container. (b) (4) batches were manufactured for the CCIT method validations: (b) (4). The following test samples were included in the method validation study:

- (b) (4)



- (b) (4)

The validation was executed by (b) (4)

The following system suitability and post check verification acceptance criteria were met for all the tests:

- (b) (4)

(b) (4)

*Reviewer's comment:* The information provided appears acceptable. The results of the CCIT method validation met the predefined acceptance criteria, which appears to indicate that the (b) (4) method may be acceptable for its intended use. The validated maximum (b) (4) of (b) (4) is within the typical (b) (4) (approximately (b) (4) used to ensure sterility of most biologic drug products.

In amendment STN 125798/0.81, Neurotech updated the following sections of the BLA to indicate that CCIT for ENCELTO stability will be performed at the Neurotech facility (not at (b) (4)) using the (b) (4) method per (b) (4) replaced the (b) (4) method per (b) (4) as well as to describe the validation of (b) (4), as applicable: Sections 2.3.P.3, 3.2.P.3.2, 3.2.P.5.2, 3.2.P.5.3, 3.2.P.5.6, 3.2.P.8.1, 3.2.P.8, and 3.2.R.2.

*Reviewer's comment:* The information provided on the primary CCS for ENCELTO appears acceptable.

#### **Shipping of ENCELTO from Neurotech facility to Distributor**

ENCELTO packaged units are stored and routinely shipped at 37 (b) (4) °C in a transport tray that can hold up to (b) (4) units of the product. A (b) (4)

(b) (4)

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

*Reviewer's comment:* The information provided appears acceptable. The results of the transport studies met the predefined acceptance criteria for temperature (37 (b) (4) °C), sterility (no growth), visual inspection (no leak or physical damage), and CCIT (pass) when worst-case transit duration (b) (4) utilizing a minimum and a maximum load were evaluated during the studies. The results appear to demonstrate the transport process from Neurotech to the distributor can maintain an integral CCS as well as the product temperature of 37 (b) (4) °C.

*Note:* While Neurotech did not provide data for a transport study performed with a (b) (4) profile, this appears to be low risk to product impact as the product is stored/transported at 37 °C, which can be representative of (b) (4) temperatures. Additionally, Neurotech assessed a maximum load of (b) (4) units, which is less than a maximum batch size of (b) (4) units that Neurotech has proposed for ENCELTO. The lack of a study with a load containing (b) (4) units (maximum batch size) appears to be a low risk as a study with (b) (4) units included the maximum units per transport tray (i.e., (b) (4) units per tray), which represents the worst-case. (b) (4) of these transport trays representing worst-case were included in the study. If the maximum batch size of (b) (4) units was distributed amongst the (b) (4) transport trays, each tray would contain approximately (b) (4) or less units, which is less than the maximum (b) (4) units per tray that was evaluated when a load of (b) (4) units was evaluated using (b) (4) transport trays.

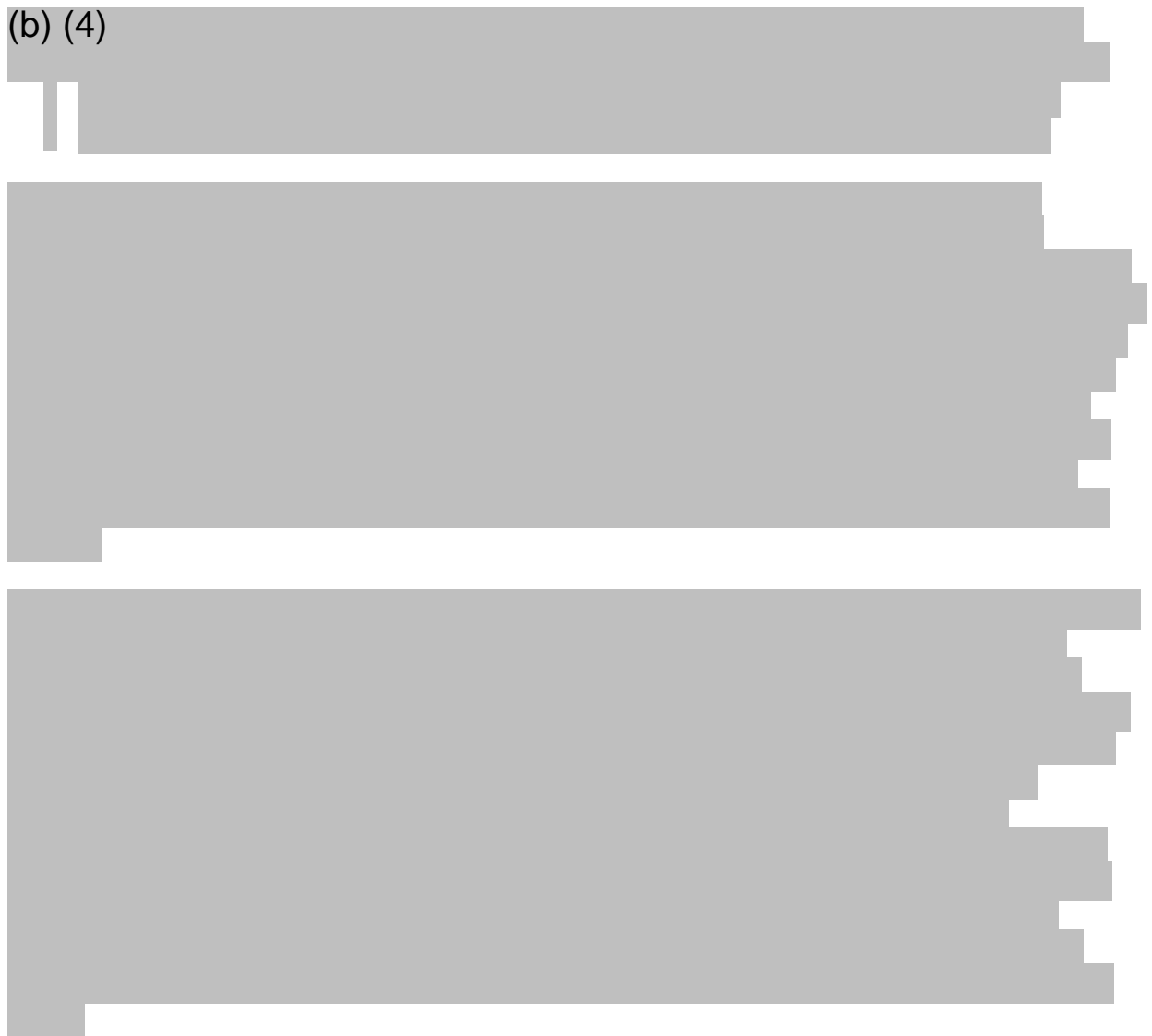
#### **Distribution – Shipment of ENCELTO from Distributor to Surgical Sites**

ENCELTO is shipped in a “NT-501 Shipping System” from the distributor (b) (4) to the surgical sites. Please see Section 3.2.P.7 (above) for a description of the shipping system. (b) (4) ENCELTO units can be shipped within the shipping system. In amendment STN 125798/0.49, Neurotech explained that if (b) (4) unit is transported, a (b) (4) is used to fill in the space where the (b) (4) ENCELTO unit would normally be placed. The shipping system includes (b) (4) (b) (4) at 37 °C and positioned (b) (4) the ENCELTO secondary CCS to maintain a temperature of 16 – 37 °C within the shipper box during transit. Neurotech stated that each shipment of ENCELTO is temperature monitored in real-time using data-loggers.

The results from study 18-00636-Therm showed that the insulated shipper with a maximum load of (b) (4) ENCELTO units maintains product temperature between (b) (4) and 37 °C when exposed to simulated (b) (4) and (b) (4) temperatures for a total of (b) (4) in each profile. Neurotech claimed that the (b) (4) transit period demonstrated that the product can be shipped anywhere in the world at the established temperature range.

(b) (4)

(b) (4)



*Reviewer's comment: The information provided for the distribution of NT-501 combination product from the distributor's storage facility to surgical centers appears acceptable. The results of the distribution studies appear to demonstrate that the NT-501 Shipping System can maintain the proposed shipping temperature of 16-37°C and provide sterility assurance of ENCELTO, as observed with an integral container closure system and passing sterility tests performed on NT-501 combination product following challenge conditions (i.e., (b) (4) temperature profiles as well as simulated distribution, respectively).*

### **3.2.P.8 Stability**

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

For ENCELTO, Neurotech proposes a shelf life of 12 weeks from the date of manufacture (i.e., date of encapsulation) when stored at (b) (4) °C. Neurotech provided the long-term stability protocol and specifications in Tables 2 and 3, which includes the following tests:

- Sterility, (b) (4) at initial (lot release) and 12 (b) (4) weeks from date of manufacture
  - Acceptance criteria: No growth (both ENCELTO and ENCELTO hold medium)
- Container closure integrity of the inner and outer containers, (b) (4) at 12 (b) (4) weeks from date of manufacture. Note: In amendment STN 125798/0.81, Neurotech revised Tables 2 and 3 to update the CCIT test method to (b) (4) performed on the outer container (see details below).
  - Acceptance criteria: Pass

Neurotech placed the (b) (4) PPQ lots (b) (4) on long-term stability. In amendment STN 125798/0.41, Neurotech stated that lot (b) (4) (labeled (b) (4)) was stored in an (b) (4) position during the (b) (4) week stability testing. Stability data supporting the proposed shelf life was provided in amendment STN 125798/0.10. The sterility and CCIT (per (b) (4)) results for all (b) (4) lots met the above acceptance criteria for all the timepoints.

In amendment STN 125798/0.81, Neurotech revised the stability program to indicate that a CCIT (b) (4) method, (b) (4) will be performed on future commercial stability batches. The CCIT will be performed on the outer container, which the applicant defined as the sterile barrier for ENCELTO. The CCIT (b) (4) per (b) (4) which was used for the (b) (4) PPQ lots and reported in the original submission, will no longer be performed.

The tests (sterility per (b) (4) and CCIT per (b) (4)) will be performed to support the 12 week shelf life for the (b) (4) stability program.

*Reviewer's comment: DMPQ defers the review of the stability testing protocols to OTP. The test results for sterility appear to support the proposed shelf life (12 weeks) met the predefined acceptance criteria.*

*Note: To support the sterility of the combination product throughout the shelf life, a CCIT (b) (4) method according to (b) (4) was performed on the (b) (4) PPQ lots. However, it was determined that (b) (4) may not be appropriate for a combination product nor uses a (b) (4) that is sensitive enough to detect (b) (4). The validated maximum (b) (4) of (b) (4) is within the typical (b) (4) (approximately (b) (4) used to ensure sterility of most biologic drug products. Therefore, a CCIT by (b) (4) method per (b) (4) was validated to be performed on future commercial stability batches as part of the (b) (4) stability program. The validated CCIT (b) (4) method was conducted on shipping validation samples and appears to indicate that the sterile barrier remains integral after shipment to the distributor as well as from the distributor to surgical sites. While no current stability results exist using CCIT by the (b) (4) method (b) (4) the existing PPQ sterility results from the 0, 12, (b) (4)-week timepoints are supportive of the 12 week shelf life. It is acceptable for both sterility and*

CCIT (b) (4) method per (b) (4) to be performed on the outer container on the future commercial product for the (b) (4) stability program.

### 3.2.A APPENDICES

### 3.2.A.1 Facilities and Equipment

## Facilities Table

<b>Facility: Manufacturing/ Testing activities</b>	<b>Inspection? Waiver? Not required?</b>	<b>Compliance check required for approval?</b>	<b>RMS-BLA entry required?</b>	<b>Comments/ Inspection history</b>
Neurotech Pharmaceuticals, Inc. 900 Highland Corporate Dr. Building 1 Suite 101 Cumberland, RI 02864  FEI: 3012545799  <ul style="list-style-type: none"> <li>• DS manufacture</li> <li>• DS release testing</li> <li>• Device design control activities</li> <li>• Storage and release testing of sterilized NT-501 pre-assembled capsule</li> <li>• DP manufacture</li> <li>• DP release testing</li> <li>• DP stability testing</li> <li>• DP labeling and packaging</li> <li>• DP batch release</li> <li>• (b) (4) storage</li> </ul>	Inspection	Yes	Yes	DMPQ/OCBQ VAI July 22 – 26, 2024
(b) (4)	RRA, 704(a)(4) records request	Yes	Yes	DMPQ/OCBQ rVAI (b) (4)
(b) (4)	Waiver	Yes	Yes	ORA VAI (b) (4)

Facility: Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments/ Inspection history
(b) (4) [REDACTED] [REDACTED] DP release testing	Waiver	Yes	Yes	ORA NAI (b) (4) [REDACTED]
(b) (4) [REDACTED] [REDACTED] • DS release testing	Not required	No	Yes	ORA VAI (b) (4) [REDACTED]
(b) (4) [REDACTED] [REDACTED] Gripper (device component) manufacturing	Not required	No	Yes	No inspection history
(b) (4) [REDACTED] [REDACTED] [REDACTED]	Not required	No	Yes	ORA VAI (b) (4) [REDACTED]
(b) (4) [REDACTED] [REDACTED] [REDACTED]	Not required	No	Yes	ORA NAI (b) (4) [REDACTED]



Facility: Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments/ Inspection history
(b) (4) [REDACTED] [REDACTED] [REDACTED]	Not required	No	Yes	ORA NAI (b) (4) [REDACTED]
(b) (4) [REDACTED] [REDACTED] • DP stability testing	Not required	No	No	ORA NAI (b) (4) [REDACTED]
(b) (4) [REDACTED] [REDACTED] [REDACTED] • Secondary (carton) packaging and labeling • DP storage • DP commercial distributor	Not required	No	Yes	ORA VAI (b) (4) [REDACTED]

\*The alternative testing sites will be used when the primary laboratory is not available.

Acronym key: DMPQ – Division of Manufacturing and Product Quality; DP – drug product; DS – drug substance; NAI – No Action Indicated; OCBQ - Office of Compliance and Biologics Quality; ORA – Office of Regulatory Affairs; RRA – Remote regulatory assessment; rVAI – Remote Voluntary Action Indicated; VAI – Voluntary Action Indicated

### Facility Design

Neurotech Pharmaceuticals, Inc. located at 900 Highland Corporate Dr., Building 1, Suite 101, Cumberland, RI is a single-product manufacturing facility. The facility manufactures ENCELTO and the NT-501 clinical products. The facility is approximately (b) (4), of which approximately (b) (4) is a dedicated modular cleanroom located on the first floor and used for the manufacturing and support operations for ENCELTO. Additionally, located on the (b) (4) floor are laboratories and office/workstations. The area

environmental classifications and the associated utilization are as follows:

Area classification	Utilization
Unclassified	General spaces such as quality control (QC) labs, development/engineering labs and offices
Controlled non-classified (CNC)	Locker room, raw material storage (warehouse), material/equipment staging, and final product storage
ISO (b) (4)	Components and equipment preparation, sterile storage (e.g., product, raw materials, equipment)
ISO (b) (4)	Background environment for ISO (b) (4) local protection units
ISO (b) (4)	(b) (4), and QC testing

In Table 2, Neurotech provided the rooms used to manufacture ENCELTO. The critical rooms and activities performed (open or closed) include:

- (b) (4)

*Reviewer's comment: The information provided appears acceptable. The cleanroom classifications appear acceptable for their respective manufacturing operations.*

### Flow Diagrams

Personnel: Personnel enter the manufacturing areas through the (b) (4)

Materials and equipment: Materials and equipment for use in the (b) (4)

Product: DS (b) (4)

Waste: Waste from ISO (b) (4)

Floor diagram for room classification of the manufacturing areas indicated that differential pressure air flow is from area of higher classification to lower classified areas.

In amendment STN 125798/0.49, Neurotech provided the most recent (executed in June 2024) cleanroom certification, which verified the differential pressures for classified areas as well as the CNC areas. The results indicated that the differential pressures for manufacturing areas were above (b) (4). Neurotech stated that the differential pressures are continuously monitored and remotely alarmed.

In amendment STN 125798/0.67, Neurotech clarified that the ISO (b) (4) areas (b) (4) are certified (b) (4) for airflow (b) (4). Additionally, the alarm limits applied for cleanrooms during differential pressures (b) (4).

*Reviewer's comment:* Neurotech provided diagrams for the flow of personnel, materials and equipment, product, and waste. The flows appear to indicate an orderly movement of personnel as well as transfer of materials, product, and waste. The flows to and from the manufacturing suite (ISO (b) (4)) are (b) (4) through dedicated airlocks. Personnel movement and material/equipment transfer through those airlocks is in sequence from CNC areas to ISO (b) (4) airlocks/corridors then to ISO (b) (4) airlocks before entering the ISO (b) (4) manufacturing area. Different gowning levels are required through the (b) (4) airlocks before entering ISO (b) (4) area. The information provided appears acceptable.

### **Contamination controls**

The manufacturing suite is dedicated to ENCELTO, and therefore, there is no risk of cross-contamination from another product. To minimize the risk of product contamination, Neurotech has implemented the following general controls:

- Defined SOPs and flows (personnel, materials, equipment, product, and waste).
- Room classification with environmental control limits.
- Facility cleaning and disinfection processes as well as the materials used for the process are defined in applicable SOPs and were challenged.
- Cleaning and disinfection of classified areas are performed according to procedures that define requirements and frequency.
- EM is performed in accordance with SOPs and defined control limits.
- The cleanroom envelope is certified (b) (4).
- The manufacturing facility, equipment, personnel, and processes were qualified/validated and are challenged routinely through aseptic media fill studies.
- Equipment preventive maintenance and calibration programs are governed, initiated, and assessed per calibration and preventive maintenance program SOP.

*Reviewer's comment:* The controls in place, which include facility design, differential

*pressure control, flows, specific gowning requirements and other measures listed above to mitigate contamination risks, appear acceptable and were evaluated during PLI.*

**Facility cleaning and disinfectant effectiveness studies**

In amendment STN 125798/0.49, Neurotech provided the following ready-to-use (RTU) disinfectants/sporicidal agents and the surfaces cleaned at the manufacturing facility.

- (b) (4)

The following routine cleaning program is used in the indicated areas:

- (b) (4)

Neurotech stated that floors, surfaces, and trash cans are cleaned (b) (4), walls are cleaned (b) (4), equipment surfaces are cleaned (b) (4), and ceilings are cleaned (b) (4).

(b) (4)



(b) (4)

*Reviewer's comment: The information provided to date appears acceptable. The results of the efficacy studies indicate that the disinfectants used in the facility met the efficacy acceptance criteria according to consensus standards. The frequency of cleaning and disinfection performed on each of the surfaces in the manufacturing areas appear acceptable. On February 10, 2025, it was communicated to Neurotech that CBER would evaluate the interim disinfectant efficacy study report as the supporting data for the BLA during the BLA review; however, due to the availability of the final disinfectant efficacy study report (early March 2025), the final disinfectant efficacy study report may be (b) (4). Therefore, Neurotech was asked not to submit the final disinfectant efficacy study report to the BLA. A final disinfectant efficacy study report containing an (b) (4) was considered low risk, because the interim study already included the evaluation of at least (b) (4).*

## Utilities

### **Purified Water**

Neurotech stated that purified water (PW) in the manufacturing facility is non-product contact and is distributed for laboratory use; however, based on responses to IRs, the applicant clarified that PW is also used for equipment cleaning. Neurotech provided a summary of the PW system. The PW system is equipped with an online (b) (4). The applicant stated that the PW is routinely sampled and tested per SOPs to ensure compliance to (b) (4).

In amendment STN 125798/0.49, Neurotech provided the summaries for the protocols used during the installation, operational, and performance qualifications (IQ/OQ/PQ) for the PW system. Neurotech certified that the IQ and OQ for the PW system were completed prior to execution of the PQ. The IQ/OQ validation was performed for a period of at least (b) (4). The PQ was performed over a period of (b) (4). During the PQ, PW samples were collected from points of use across the PW (b) (4) as well as from the (b) (4). The following tests were conducted on the collected the samples and met the indicated acceptance criteria established according to (b) (4) with no deviation occurring during the qualification.

- (b) (4)

(b) (4)

PW is routinely monitored for (b) (4) and (b) (4) is sampled (b) (4) at the (b) (4) of use. (b) (4) is routinely monitored for (b) (4) while (b) (4) are tested (b) (4). The action limits are set at the acceptance criteria applied during qualification, except for (b) (4) (action limit (b) (4)). Alert levels are set lower than the action limits.

*Reviewer's comment: The information provided for purified water system appears acceptable. The results for the PQ met the predefined acceptance criteria, which appear to be in accordance with industry standards (b) (4) and the same criteria are applied for routine monitoring. PW is not used for manufacturing operations but is used for equipment and facility cleaning as well as for (b) (4). Cleaned equipment used for aseptic processes is sterilized.*

## **Gas Systems**

### **Compressed Air**

Neurotech stated that compressed air (CA) in the manufacturing facility is non-product contact. The CA system is used to (b) (4) manufacturing process equipment as well as for raw material (b) (4) operations and (b) (4). Neurotech provided a summary of the CA system, which includes (b) (4) at the point of use. The applicant stated that CA is routinely sampled and tested per SOPs.


In amendment STN 125798/0.49, Neurotech provided the summaries for the protocols used during the IQ, OQ, and PQ for the CA. Neurotech certified that the IQ and OQ for the CA were completed prior to execution of the PQ. The IQ/OQ validation was performed over a period of (b) (4) months. The PQ was performed over a period of (b) (4) days. The following tests were conducted and met the indicated acceptance criteria, and no deviation with impact to the results or qualification occurred.

- (b) (4)





(b) (4)

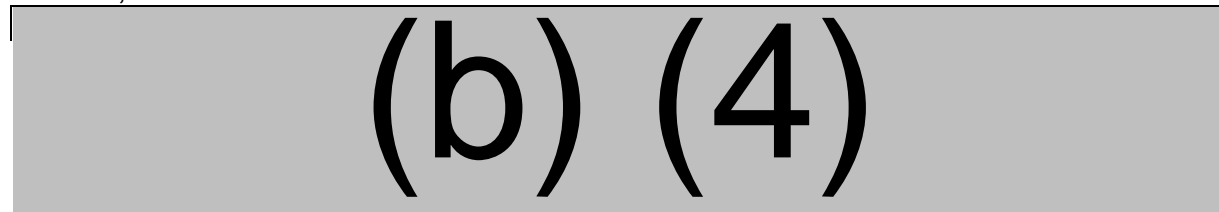


**Reviewer's comment:** *The information provided for the gas systems appears acceptable. The results for the PQ met the predefined acceptance criteria, which appear to be in accordance with industry standards and the same criteria are applied for routine monitoring. The utilities are routinely tested, and the defined action limits appear to be within industry standards. Utilities excursions are handled as quality event deviations per approved SOP (SOP-1013, "Quality Event Process"). Neurotech's commitment to revise SOP-2086 "Process for Sampling and Monitoring of the Gas Systems at the Cumberland Manufacturing Facility" to include routine (b) (4) testing at the (b) (4) point of use appears acceptable.*

**Heating, Ventilation, and Air Conditioning (HVAC): Qualification and routine monitoring**

The HVAC system consists of following air handling units (AHUs) also referred to as RAHUs,

(b) (4)





- (b) (4)

In amendment STN 125798/0.49, Neurotech explained that EM excursions (exceedance of limits) result in an investigation per site procedures. Microbial identification is performed on all recovered viables.

*Reviewer's comment: The information provided for the HVAC and EM appears acceptable. While the acceptance criterion of non-viable particulates (b) (4) for the EMPQ of ISO (b) (4) areas under (b) (4) conditions is higher than expected for an ISO (b) (4) area (b) (4) the EMPQ results met the acceptance criterion. Additionally, the limits for routine EM of an ISO (b) (4) area (b) (4) as well as the results of the EM during the manufacture of the (b) (4) PPQ lots are in accordance with industry standards and regulatory guidance (i.e., FDA Aseptic Processing Guidance, (b) (4) and ISO (b) (4) . The EMPQ in ISO (b) (4) ISO (b) (4) areas included (b) (4) conditions. The EMPQ in ISO (b) (4) areas was performed under (b) (4) conditions only; EMPQ under (b) (4) conditions in ISO (b) (4) areas was not performed. However, the EM data collected during the manufacture of the PPQ lots appear to support the qualification of the ISO (b) (4) areas. The EM data during the PPQ and the EM results of the media fill studies appear to demonstrate the classified areas operate in a state of control to manufacture ENCELTO.*

## Equipment

### Process Equipment

Neurotech stated that all systems/equipment are dedicated to ENCELTO. In Section 3.2.S.2.3, Neurotech provided the product contact materials used to manufacture the (b) (4) . Those materials include (b) (4) .

The applicant stated that the materials are single-use and supplied sterile. In amendment STN 125798/0.49, Neurotech added details for the single-use materials used in the (b) (4) of (b) (4) adhesive to section 3.2.P.2.3 (Tables 5 and 6).

In Table 12, Neurotech provided a list the product contact components/ equipment used in the encapsulation process to manufacture ENCELTO. The information provided includes the details of component/equipment designated asset number, description, process step and use, material of construction, and cleaning/sterilization method. The following is a summary of the product contact components/equipment used in the fill and finish process during the manufacture of ENCELTO.

(b) (4)

(b) (4)

In Tables 11 and 13, Neurotech provided a list non-product contact equipment used in the manufacture of ENCELTO. The following is a summary of the critical non-product contact equipment.

(b) (4)

#### **Equipment Qualification**

(b) (4)

In amendment STN 125798/0.49, Neurotech provided the protocols for the qualification of (1)(b) (4) which are used for (b) (4) activities to manufacture the (b) (4), which is used during cell encapsulation operations as well as packaging of ENCELTO. Neurotech stated that installation and operation were in accordance with design intent, manufacturer's recommendations, and requirements. The protocols listed the IQ/OQ/PQ requirements as well as the tests

performed including the those listed below. Neurotech stated that all acceptance criteria were met with no protocol discrepancies or quality events observed.

- (b) (4)

*Reviewer's comment: The information provided for (b) (4) qualification appears acceptable. The qualification results met the predefined acceptance criteria, which appears to demonstrate the (b) (4) operate at the expected conditions during the manufacture of ENCELTO. (b) (4) studies were evaluated during the PLI of the Neurotech facility.*

### **Cell Culture incubators**

In amendment STN 125798/0.49, Neurotech provided the protocols for the qualification of each of the (b) (4) which are used for (b) (4) to manufacture the (b) (4). In amendment STN 125798/0.67, Neurotech stated that the (b) (4) are identical (i.e., (b) (4), each containing (b) (4) and each shelf containing (b) (4) brackets).

The qualification protocols for the (b) (4) included the initial IQ/OQ as well as the (b) (4) PQ. Neurotech stated that installation and operation were in accordance with design intent, manufacturer's recommendations, and requirements. The functional operations tested during IQ/OQ included (b) (4), and (b) (4)

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

Reviewer's comment: The qualification results met the predefined acceptance criteria, which appears to demonstrate the incubators can operate at the expected conditions during the manufacture of ENCELTO.

It is noted that the acceptance criteria for assessment of temperature, (b) (4) (b) (4) recovery were not provided for the qualification studies. This poses a low risk to the product as the (b) (4) temperature and (b) (4) are continuously monitored and alarmed, and Neurotech noted that the acceptance criteria were met for those parameters (temperature, (b) (4) ), which are information only.

(b) (4)

(b) (4)

(b) (4)





(b) (4)

### **Computer systems**

Neurotech provided a list of computer systems that have direct impact on the manufacture of ENCELTO. The list included the qualification document numbers for each system. The systems include (b) (4)

*Reviewer's comment: Qualification of the major computer systems were reviewed during the PLI.*

## **3.2.R REGIONAL INFORMATION**

### **ENCELTO Device Constituent (NT-501 PAC)**

#### **3.2 Manufacturers**

The NT-501 PAC (device constituent of ENCELTO) is manufactured (i.e., assembled) at (b) (4)

*Reviewer's comments: See section 3.2.A.1 for the details of the facility.*

### **Quality System**

The ENCELTO combination product is manufactured at Neurotech. Neurotech stated that it implemented a drug cGMP-based streamlined operating system in accordance with 21 CFR 4.4(b)(1) whereby the following provisions from the medical device Quality System Regulation (21 CFR 820) have been applied to the manufacture of NT-501 PAC:

- 21 CFR 820.20 Management Responsibility
- 21 CFR 820.30 Design Controls
- 21 CFR 820.50 Purchasing Controls
- 21 CFR 820.100 Corrective and Preventive Action

Neurotech provided summaries of the procedures implemented at Neurotech to comply with each applicable quality system regulation provision.

*Reviewer's comment: Neurotech's quality system was evaluated during the PLI conducted July 22 – 26, 2024.*

(b) (4)

