

**CBER CMC BLA Review Memorandum**

**BLA STN 125798/0**

**ENCELTO / revakinagene taroretccl-lwey**

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**1. BLA#:** STN125798/0

**2. APPLICANT NAME AND LICENSE NUMBER**

Neurotech Pharmaceuticals Inc.

License Number: 2321

**3. PRODUCT NAME/PRODUCT TYPE**

Proper/USAN: revakinagene taroretcel-lwey

Proprietary Name: ENCELTO

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

- a. Pharmacological category: Allogeneic encapsulated cell-based gene therapy
- b. Dosage form: One single-use implant containing 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotrophic factor (rhCNTF)
- c. Strength/Potency [200,00-(b) (4) cells/drug product; (b) (4)
- d. Route of administration: surgical intravitreal implant
- e. Indication(s): Treatment of adults with idiopathic macular telangiectasia (MacTel) type 2

**5. MAJOR MILESTONES**

<b>Original Submission</b>	04-18-2024
<b>Application Filed</b>	06-17-2024
<b>Mid-Cycle communication</b>	08-15-2024
<b>Late-Cycle Meeting</b>	10-07-2024
<b>Major Amendment</b>	10-16-2024
<b>Advisory Committee meeting</b>	Not Held
<b>Inspections</b>	Pre-License Inspection (PLI): 07/22/2024-07/26/2024
<b>PDUFA Action Date Original</b>	12/17/2024
<b>Final</b>	03/18/2025

## 6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Carolina Panico (CP), CBER/OTP/OCTHT/DCT2/TEB2	3.2.S Drug Substance 3.2.P Drug Product 3.2.R.1 Executed Batches 3.2.R.2 Methods validation package
Kyung Sung (KS), CBER/OTP/OCTHT/DCT1/CTTB	3.2.A.2 Adventitious Agents Safety Evaluation 3.2.R Combination Product 3.2.R.3 Device
Shirin Marfatia (SM), CBER/OTP/OCTHT/DCT2/TEB2	3.2.S.2.2 Description of Manufacturing Process 3.2.S.2.3 Control of Materials 3.2.P.2.4 Container Closure System 3.2.P.4.6 Novel Excipients 3.2.P.6 Reference of Standards Materials 3.2.P.7 Container Closure System
Edhriz Siraliev-Perez, CBER/OGT/DGT1/GTB1	3.2.S.1.2 Structure 3.2.S.1.3 General Properties 3.2.S.2.3 Control of Materials 3.2.S.3.2 Impurities
Brychan (Brandy) Clark, CBER/OTP/OCTHT/DHT/HTRS	3.2.A.2 Adventitious Agents Safety Evaluation (Donor eligibility)
Cinque Soto (CS), CBER/OTP/OCTHT/DCT1 Sandip De (SD), CBER/OTP/OCTHT/DCT2/TVBB	3.2.A.2 Adventitious Agents Safety Evaluation
Wojtek Tutak (WT), CBER/OTP/OCTHT/DCT2/TEB2	3.2.R.3 Device (Biocompatibility)
Andrey Sarafanov (AS), CBER/OTP/OPPT/DH/HB2	3.2.P.2.4 Container Closure System 3.2.P.2.6 Compatibility 3.2.P.7 Container Closure System

## 7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations (Yes/No)
Alexander Beylin, OHT1/DHT1A/THTA3	3.2.R.3 Device (Gripper)	Yes

## 8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
8/19/2024	125798/26	Information request (IR)#1 related to the consumables used for the manufacturing; sampling plan; endotoxin specifications; environmental assessment categorical exclusion. RESOLVED
9/4/2024	125798/32	IR#2 related to the (b) (4) information included in section 3.A.2; (b) (4) adhesive used for device constituent. RESOLVED
9/19/2024 12/11/2024	125798/37 125798/70	IR# 3 related to (b) (4) raw materials (b) (4) testing; (b) (4) testing; (b) (4) impurities; biocompatibility device constituent; cumulative (b) (4). RESOLVED
10/11/2024	125798/47	IR#4 related to DP stability protocols, (b) (4); Endothelial- serum-free medium (Endo-SFM); USAN name and proper name suffix. RESOLVED.
10/16/2024	12798/48	IR#5 related to cumulative (b) (4). RESOLVED.
11/08/2024	12798/62	IR#6 related to pre-assembled capsule (PAC) (b) (4) testing; adventitious testing raw materials; container closure system and packaging. RESOLVED.
11/15/2024	125798/63	IR#7 related to the quality agreements status with (b) (4) Medical Devices. FOLLOW-UP IR#8.
11/20/2024	125798/66	IR#8 related to the status quality with (b) (4) Medical Devices. RESOLVED.
2/12/2015	125798/87	IR#9 related to the sampling plan for drug product (DP) release testing; batch formula for commercialization. RESOLVED.

**9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)**

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
Master File (MF) (b) (4)	(b) (4)	(b) (4)	Yes	Information pertinent to Endo-SFM was reviewed and documented in section 3.2.P.4 of the memo.
MF(b) (4)	(b) (4)	(b) (4)	Yes	Information pertinent to (b) (4) testing of the DS.
MF(b) (4)	(b) (4)	(b) (4)	Yes	Information pertinent to (b) (4) for testing adventitious agents was reviewed and discussed in section 3.2.A of this memo.

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

ENCELTO is a single use, allogeneic encapsulated cell-based gene therapy combination product that contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells (RPE) expressing recombinant human ciliary neurotrophic factor (rhCNTF). The pre-assembled capsule (PAC) used to encapsulate the cells is opaque, white to off-white, semipermeable and consists of a (b) (4) hollow fiber membrane (HFM) surrounding a polyethylene terephthalate (PET) scaffold yarn. The PAC is sealed at both ends and has a titanium loop on one end. The titanium anchor loop is connected to a titanium gripper that holds ENCELTO in the inner container of the primary container closure system. The gripper is also used to facilitate surgical placement and retrieval (if medically necessary). ENCELTO width is  $1.2 \pm 0.1$  mm, length is  $6.1 \pm 0.4$  mm, and its internal diameter is  $0.88 \pm 0.02$  mm and has a 12-week shelf-life when stored at 16-37°C. The recommended dose is one implant containing 200,000 to 440,000 cells per affected eye to treat adults with idiopathic macular telangiectasia (MacTel) type 2.

An Investigational New Drug application (IND) 10931 was submitted by Neurotech Pharmaceuticals Inc. (also referred to as Neurotech or the Applicant) on February 24, 2003 for the study of ENCELTO for treatment of (b) (4) macular telangiectasia

(MacTel) type 2. ENCELTO was granted Orphan Drug designation March 29, 2012, and FAST TRACK designation December 17, 2018, for (b) (4) MacTel 2. The Biologics License Application (BLA) for ENCELTO for the treatment of MacTel 2 was submitted on April 18, 2024. The BLA was filed June 17, 2024, with a Priority Review designation. A Major Amendment was declared on October 16, 2024 due to Neurotech's submission of substantial amount of new manufacturing and facility information not previously submitted to or reviewed by FDA.

The manufacturing control strategy for ENCELTO (also referred to as NT-501 in memorandum, which was the name for ENCELTO during product development and investigational studies) includes: (1) chain of identity and chain of custody, (2) raw material and reagent qualification programs, (3) in-process monitoring and control testing, (4) validation of manufacturing process, and (5) release testing.

The manufacturing process of ENCELTO is a continuous process from (b) (4) cell encapsulation to obtain the final product, to packaging and labeling. There are no hold times, intermediates, or drug substance (DS) release. Briefly, the cells used in ENCELTO were derived from a (b) (4) NTC-201-6A stable cell line. The NTC-2-1-6A (b) (4)

Because the (b) (4) was derived from a (b) (4), prior to the establishment of the donor eligibility regulatory requirements outlined in 21 CFR 1271, subpart C, the Applicant performed a comprehensive adventitious agent risk assessment to assess the risk of communicable diseases. (b) (4) derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents. Critical process parameters and critical quality attributes are established through process characterization and validation studies. Controls are implemented throughout the manufacturing process to support process consistency. In-process controls include (b) (4)

The manufacturing of the device constituents of ENCELTO, which are the PAC and gripper, is performed using semi-automated manufacturing equipment and managed through the design control process, with device specifications determined by design inputs including essential performance requirements. PAC release testing includes assessment of (b) (4). Additionally, the gripper is released based on (b) (4) testing.

Lot release testing is performed on the final ENCELTO product, except for (b) (4) which is performed on the (b) (4). Product release testing

on the drug product includes appearance (visual inspection), rhCNTF protein expression using (b) (4), pH, sterility, endotoxin, mycoplasma, viability, strength ((b) (4) potency (b) (4)), and identity (rhCNTF expression using (b) (4)).

The CMC concerns identified during the review included insufficient information related to the following: identity testing of the raw materials used in the manufacturing of the (b) (4) container closure system, and stability studies protocols. The CMC issues listed above were resolved through information requests.

Concerns related to (b) (4) validation studies were identified during the review of this submission and require post market commitments (PMC). The two PMC studies agreed upon with the Applicant on February 27, 2025, include a (b) (4)

In conclusion, the BLA submission review and pre-license inspection confirmed that the manufacturing processes is in a state of control and capable of producing a consistent drug product of acceptable quality that satisfies FDA requirements for identity, purity, and potency. The BLA can be approved under the condition that the Applicant commits to perform the PMC discussed above.

## B. RECOMMENDATION

### I. APPROVAL

a. Manufacturing Facilities are provided below.

Name/Address	Responsibility
Neurotech Pharmaceuticals, Inc., 900 Highland Corporate Drive Building #1, Suite #101 Cumberland, RI 02864 FEI: 3012545799 DUNS: 117685116	Manufacture of the DS and DP; DS testing (In-Process Controls) and DP release; (b) (4) storage
(b) (4)	(b) (4) Testing
(b) (4)	(b) (4)

(b) (4)

b. PMCs

PMC#1: Neurotech commits to perform a (b) (4) validation study that includes a (b) (4)

The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by July 31, 2025.

PMC#2: Neurotech commits to perform (b) (4), (b) (4)

The final report will be submitted as a “Postmarketing Commitment - Final Study Report” by July 31, 2025

c. Lot release protocols

The Applicant did not submit any information related to lot release protocols (LRP) or waiver in the original BLA. An information request was sent requesting LRP on June 12, 2024. The Applicant provided the first draft of LRP in Amendment 13 (dated July 3, 2024). The final revision of the LRP was included in Amendment 58 (dated October 30, 2024).



## II. COMPLETE RESPONSE (CR)

Not Applicable (N/A).

## III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Carolina Panico, MD, PhD CMC Reviewer CBER/OTP/OCTHT/DCT2/TEB2	Concur	
Kyung Sung' PhD CMC Reviewer CBER/OTP/OCTHT/DCT1/CTTB	Concur	
Shirin Marfatia, PhD CMC Reviewer CBER/OTP/OCTHT/DCT2/TEB2	Concur	
Alyssa Kitchel, PhD Branch Chief CBER/OTP/OCTHT/DCT2/TEB2	Concur	
Laura Ricles, PhD Division Director CBER/OTP/OCTHT/DCT2	Concur	
Steven Oh, PhD Deputy Office Director CBER/OTP/OCTHT	Concur	
Heather Lombardi, PhD Office Director CBER/OTP/OCTHT	Concur	

**Review of CTD**  
**Table of Contents**

3.2.S DRUG SUBSTANCE .....	11
3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties .....	11
3.2.S.2 Manufacture.....	13
3.2.S.2.1 Manufacturer(s).....	13
3.2.S.2.2 Description of Manufacturing Process.....	14
3.2.S.2.3 Control of Materials .....	22
3.2.S.2.4 Controls of Critical Steps and Intermediates .....	40
3.2.S.2.5 Process Validation and/or Evaluation.....	44
3.2.S.2.6 Manufacturing Process Development .....	45
3.2.S.3 Characterization .....	45
3.2.S.3.1 Elucidation of Structure and Other Characteristics .....	45
3.2.S.3.2 Impurities.....	47
3.2.S.4 Control of Drug Substance .....	49
3.2.S.4.1 Specification(s) and 3.2.S.4.5 Justification of Specification(s) .....	49
3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures.....	49
3.2.S.4.4 Batch Analyses.....	51
3.2.S.5 Reference Standards or Materials .....	53
3.2.S.6 Container Closure System.....	54
3.2.S.7 Stability .....	55
3.2.S.7.1 Stability Summary and Conclusion and 3.2.S.7.3 Stability Data .....	55
3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment .....	55
3.2.P DRUG PRODUCT .....	55
3.2.P.1 Description and Composition of the Drug Product.....	55
3.2.P.2 Pharmaceutical Development.....	56
3.2.P.2.1 Components of the Drug Product.....	56
3.2.P.2.2 Drug Product .....	58
3.2.P.2.3 Manufacturing Process Development .....	60
3.2.P.2.4 Container Closure System .....	65
3.2.P.2.5 Microbiological Attributes .....	66
3.2.P.2.6 Compatibility.....	66
3.2.P.3 Manufacture.....	69
3.2.P.3.1 Manufacturer(s).....	69
3.2.P.3.2 Batch Formula .....	70
3.2.P.3.3 Description of Manufacturing Process.....	71
3.2.P.3.4 Controls of Critical Steps and Intermediates .....	77
3.2.P.3.5 Process Validation and/or Evaluation.....	78
3.2.P.4 Control of Excipients.....	82
3.2.P.4.1 Specifications .....	82
3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures.....	86
3.2.P.4.4 Justification of Specifications .....	86
3.2.P.4.5 Excipients of Human or Animal Origin.....	87
3.2.P.4.6 Novel Excipient.....	87
3.2.P.5 Control of Drug Product.....	88
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) .....	88
3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures.....	92
3.2.P.5.4 Batch Analyses.....	108
3.2.P.5.5 Characterization of Impurities.....	109

3.2.P.6 Reference Standards or Materials .....	110
3.2.P.7 Container Closure System .....	116
3.2.P.8 Stability .....	128
3.2.P.8.1 Stability Summary and Conclusion.....	128
3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment .....	131
3.2.P.8.3 Stability Data .....	132
3.2.A APPENDICES .....	133
3.2.A.1 Facilities and Equipment.....	133
3.2.A.2 Adventitious Agents Safety Evaluation .....	144
3.2.A.3 Novel Excipients .....	149
3.2.R Regional Information (USA) .....	149
3.2.R.3 Device .....	151

### **List of Figures**

Figure 1. (b) (4) .....	12
Figure 2. (b) (4) .....	13
Figure 3A. (b) (4) .....	16
Figure 4. (b) (4) .....	29
Figure 4. (b) (4) .....	46
Figure 6. (b) (4) .....	56
Figure 7. (b) (4) .....	59
Figure 8. Inner container of the DP container closure system .....	65
Figure 9. Outer container of the DP container closure system .....	66
Figure 10. Inner container filling.....	73
Figure 11. (b) (4) .....	73
Figure 12. Positioning of the PAC on the injector .....	74
Figure 13. PAC separated from the load hub .....	74
Figure 14. (b) (4) tool.....	74
Figure 15. Adhesive applicant.....	75
Figure 16. Securing the DP in the inner container. ....	75
Figure 17. (b) (4) .....	76
Figure 18. (b) (4) .....	76
Figure 19. (b) (4) .....	85
Figure 20. (b) (4) .....	113
Figure 27. NT-501 Shipping System (b) (4) shipper system).....	125
Figure 28. (b) (4) Corepack showing Label Placement .....	125
Figure 29. Room Classification with (b) (4) Airflow Direction .....	135
Figure 30. Personnel flow .....	136
Figure 31. Material Flow .....	137
Figure 32. Drug product Flow .....	138
Figure 33. Drug product Flow .....	139
Figure 34. Mechanical HVAC Colored Plan.....	140
Figure 35. Equipment Layout.....	141
Figure 36. NT-501 capsule (A) and cutaway representation of the capsule (B) .....	152
Figure 37. NT-501 PAC assembly .....	152

Figure 38. Image of NT-501 fixation loop.....	155
Figure 39. Image of NT-501 gripper.....	156
Figure 40. Image of (b) (4) sub-assembly .....	157
Figure 41. Image of the final PAC assembly.....	158
Figure 42. Image of the PAC sterilization packaging .....	158
Figure 43. Schematic overview of Neurotech’s Design Control process .....	161
Figure 44. NT-501 PAC manufacturing process flow diagram.....	170
Figure 40. Carton (corepack) Label .....	177
Figure 41. Container Label .....	178

## **Module 3**

### **3.2.S DRUG SUBSTANCE<sup>1</sup>**

#### **3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties**

(b) (4)



43 pages determined to be not releasable: (b)(4)

(b) (4)

### 3.2.P DRUG PRODUCT

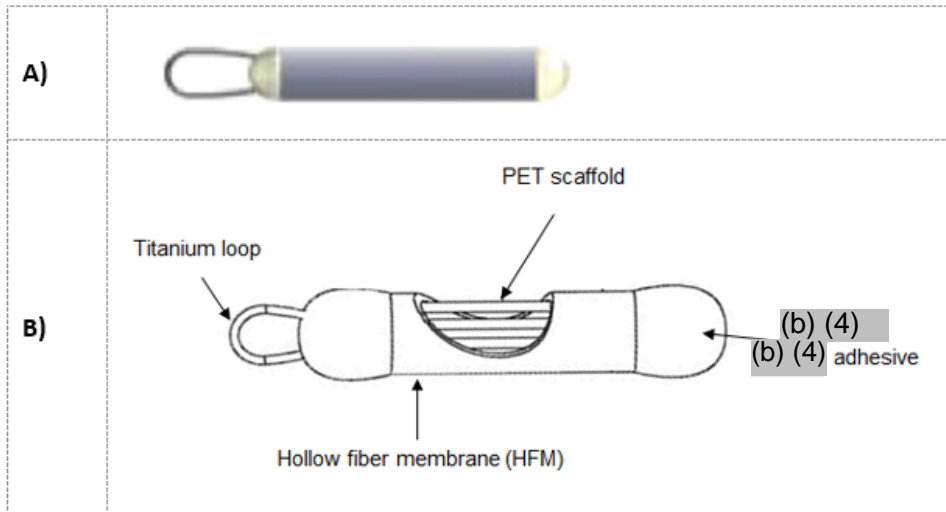
#### 3.2.P.1 Description and Composition of the Drug Product

*Reviewed by CP*

ENCELTO is an implant comprised of a pre-assembled capsule (PAC) containing 200,000 to 440,000 allogeneic retinal pigment epithelial cells (RPE) expressing recombinant human ciliary neurotrophic factor (rhCNTF) (b) (4), also referred to as NTC-201-6A cells.

The PAC consists of a titanium anchor loop, (b) (4) hollow fiber membrane (HFM) containing an internal scaffold of (b) (4) polyethylene terephthalate (PTE) scaffold yarn. The PAC is sealed with methacrylate adhesive (b) (4). The titanium anchor loop is used to facilitate placement and retrieval (if medically necessary) of the implant and is attached to one end of the semi-permeable capsule. Figure 6A-B below provides an image and a schematic representation of ENCELTO.

ENCELTO width is  $1.2 \pm 0.1$  mm, length is  $6.1 \pm 0.4$  mm, and its internal diameter is  $0.88 \pm 0.02$  mm. Placement in the surgical insertion procedure requires a (b) (4) -3.0 mm incision in the pars plana.



**Figure 6. Pre-assembled capsule (PAC)**

### 3.2.P.2 Pharmaceutical Development

#### 3.2.P.2.1 Components of the Drug Product

##### 3.2.P.2.1.1 Drug Substance

(b) (4)

[Redacted content]

(b) (4)

(b) (4)

(b) (4)

(b) (4)

### 3.2.P.2.1.2 Excipients

#### *Reviewed by CP*

Endothelial-serum free medium (Endo-SFM)

Endo-SFM is used for the (b) (4) DP hold media in the primary container closure system. The medium is purchased from (b) (4) that holds a master file in CBER ((b) (4)). The Applicant provided the letter of authorization in section 1.4.2 of the BLA. The volume of hold Endo-SFM used in the container closure as hold media of DP is (b) (4). Please refer to Section 3.2.S.2.3 and Section 3.2.P.4 for additional information on excipients.




### 3.2.P.2.2 Drug Product

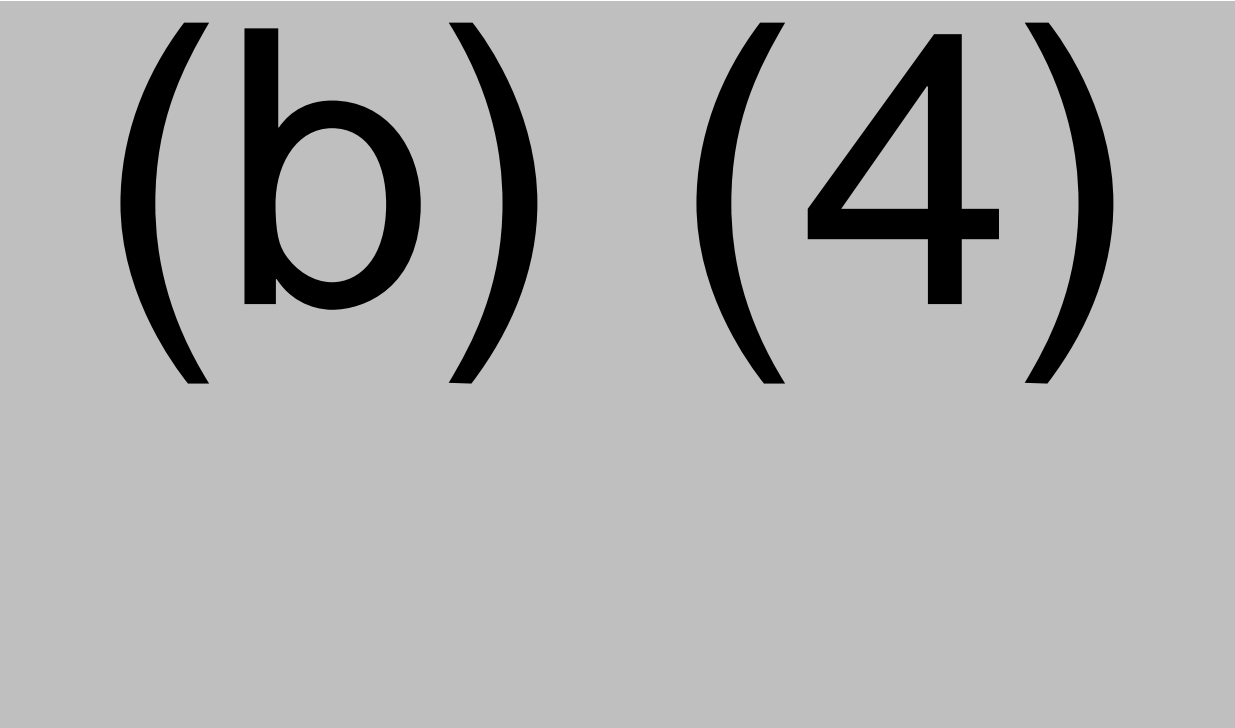
#### 3.2.P.2.2.1 Formulation Development

*Reviewed by CP*

The manufacturing process of ENCELTO (also referred to as NT-501 in this review) is a continuous process from (b) (4) cells encapsulation, packaging and labeling. Briefly, the DS (b) (4)



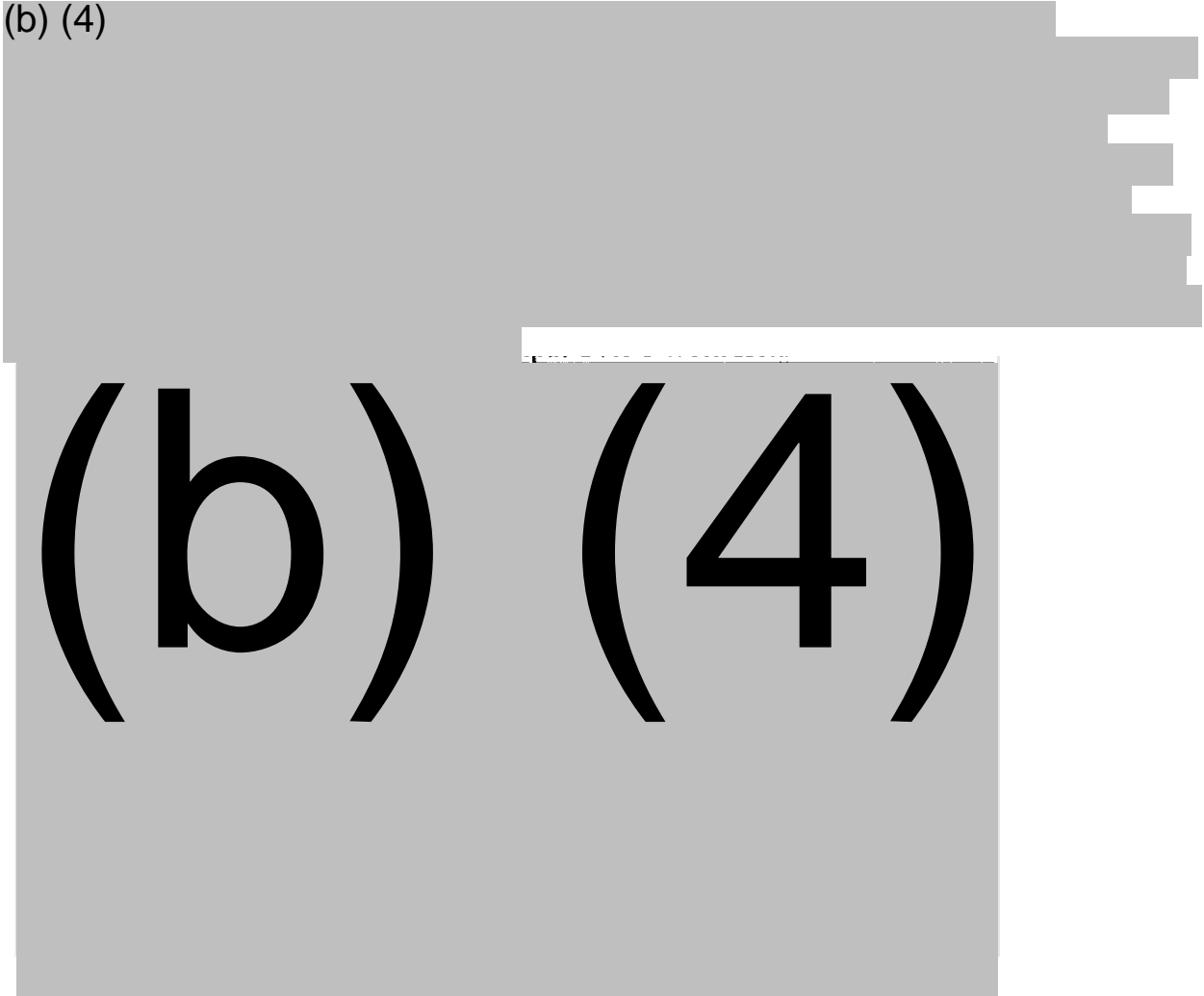
During the manufacturing process development there were minimal changes in the manufacturing process of the DP from clinical Phase 1 through Phase 3 and commercial (refer to Section 3.2.P.2.3 for details on manufacturing process development). Specifically, a (b) (4) was established, new (b) (4) and a new (b) (4) of the (b) (4) was implemented. A summary of the DP formulation development is provided in Table 20 below.



In addition, minor changes to the semi-automated process were also implemented. Please refer to section 3.2.P.2.3 below for more details on the semiautomated process.


(b) (4)

(b) (4)



(b) (4)

(b) (4)



#### **3.2.P.2.2.2 Overages**

Not Applicable (N/A).

#### **3.2.P.2.2.3 Physicochemical and Biological Properties**

*Reviewed by CP*

The DP is a biologic-device combination product. The DP is held in Endo-SFM (b) (4) and stored at 37 C (b) (4) with demonstrated stability in the final container closure (Section 3.2.P.8.3). The biological properties of the DP are monitored on stability and the stability data presented in Section 3.2.P.8.3 confirms that the biological activity of the product is maintained. The biological properties of the DS are described in Section 3.2.S.3.1.

### 3.2.P.2.3 Manufacturing Process Development

*Reviewed by CP*

The manufacturing process development of ENCELTO throughout the clinical studies, from the Phase 1 clinical study to the end of the Phase 3 clinical study, and in preparation for commercialization have been conducted at the Neurotech manufacturing facility located in Cumberland, RI.

The manufacturing process consists of (b) (4)

This aseptic DP (b) (4)  
operation is semi-automated and comprises (b) (4) process steps:

(b) (4)

Minor changes to the semi-automated process have occurred throughout NT-501 development. Table 21 summarizes the changes to the manufacturing process, clinical to commercial.

**Table 21. Changes between the clinical and commercial manufacturing process**

(b) (4)

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

(b) (4)

**Reviewer's comment (CP):** *The changes between the clinical and commercial manufacturing process of the DP included semi-automation of the (b) (4)*

*. I agree with the Applicant in that the changes were minor and did not impact the quality of the DP over time.*

### **Analytical Methods Development**

#### *Reviewed by CP*

Throughout the development of ENCELTO, changes have been made to the analytical methods. Refer to Table 22 illustrates the changes made prior to Phase 3 clinical manufacturing and to Table 23 changes made after Phase 3 clinical manufacturing in support of commercial manufacturing.

**Table 22. Analytical Method Development Summary Prior to Phase 3 Clinical Manufacturing**

(b) (4)

(b) (4)

**Table 23. Analytical Test Method Development Summary After Phase 3 Clinical Manufacturing**

(b) (4)

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

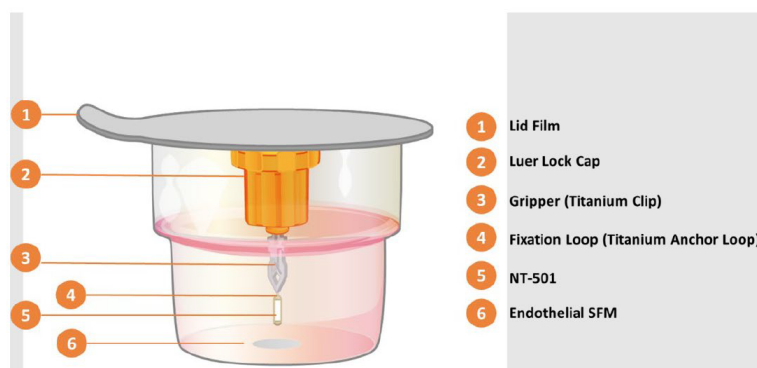
(b) (4)

**Reviewer's comment (CP):** The changes to the methods from product development to commercial process (shown in the tables 22 and 23 above) are acceptable as they include the establishment of compendial methods and of the viability and potency assay used for release.

### 3.2.P.2.4 Container Closure System

*Reviewed by SM*

The DP primary container closure system (CCS) is comprised of an inner container and an outer container. The inner container consists of polycarbonate container and has an upper and lower compartment. The lower compartment contains Endo-SFM and the NT-501 secured to the Luer lock cap by the implant gripper. The upper compartment remains dry and includes the female Luer lock opening allowing access to the locking Luer lock cap. A foil composite lid film (foil film) is sealed to the primary package. This seal is gas impermeable. The inner container set up is shown in Figure 8 below.



**Figure 8. Inner container of the DP container closure system**



The sealed inner container is placed into a (b) (4) polypropylene outer container. The outer container is sealed with a foil composite lid film (foil film) which provides container closure integrity protection during storage and shipping of the DP. This seal is gas impermeable. The outer container is shown in Figure 9 below.



**Figure 9. Outer container of the DP container closure system**

**Reviewer's comment (SM):** Refer to section 3.2.P.7 and 3.2.P.8 for information on the packaging components, storage and shipping, container closure integrity and stability studies.

### **3.2.P.2.5 Microbiological Attributes**

*Reviewed by CP*

Aseptic processes are implemented in the manufacturing of ENCELTO to prevent microbial contamination of the DP, the excipient Endo-SFM and the primary CCS. Briefly, study R0276 was conducted to demonstrate the Endo-SFM hold media (b) (4), under the proposed shelf-life storage conditions. In addition, study P025 was executed to demonstrate the recovery of microorganisms, if present, from unsealed DP. Study PQ-Q2304086 was performed by contract test lab, (b) (4) to demonstrate primary container closure integrity and was performed according to (b) (4) and (b) (4). Please refer to the DMPQ memo for the review of the aseptic processes and the studies listed above in this section.

### **3.2.P.2.6 Compatibility**

(b) (4)



methods. These concerns were communicated to the Applicant through two (2) information requests (dated September 12, 2024 and September 26, 2024). In the response to first information request, (Amendment 37, dated September 19, 2024), the Applicant informed that (b) (4) was not calculated and thus, not applied to the data in the (b) (4) study described in Report J12626, and LOQ was not provided by the contractor (b) (4) that performed the study. At the same time, the Applicant provided the following three (3) additional reports: (b) (4)

(b) (4), and the Toxicological Risk Assessment of NT-501 Intraocular Implant. In the response to second information request (Amendment 44, dated October 4, 2024), the Applicant provided a summary of the reports. However, the relevance of the information included in the original information in relation to the new reports was unclear. During the late-cycle meeting with the Applicant (held October 7, 2024), the Applicant clarified that the new (b) (4) study data were to replace and not to support the data submitted in the original BLA. As that would trigger new round of review, a third information request was sent on October 11, 2024 asking the Applicant to summarize the new data due to the large volume and short time remaining on the review clock. The Applicant provided the requested summary in Amendment 48 (dated October 16, 2024).

Upon review of the new data, the consult determined that the new (b) (4) study on the (b) (4) (conducted by (b) (4) according to Annex A in ISO 10993-1:2018, ISO 10993-12:2021, ISO 10993-18:2020, and the FDA's Guidance for Industry Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices: Part 1: Evaluation and Testing within a Risk Management Process (September 2023)) used an (b) (4)

Toxicological assessment concluded that the NT-501 device is "unlikely to pose a significant risk for patients".

**Overall Reviewer's Assessment (CP):** A consult was requested August 2, 2024, for the assessment of the (b) (4) data. The consult, Dr. Andrey Sarafanov

(CBER/OTP/OPPT/DH/HB2), provided the (b) (4) analytical data review assessment February 2, 2025. Dr. Sarafanov indicated that, from the analytical perspective, the cumulative (b) (4) data are acceptable and BLA is approvable and deferred the toxicological risk assessment of the (b) (4) results to toxicological reviewer, Dr. Ernesto Moreira. Dr. Moreira concluded that the toxicological risk assessment is adequate to supports the safe use of ENCELTO under the proposed conditions and clinical use.

### 3.2.P.3 Manufacture

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

*Reviewed by CP*

Please refer to Table 24 below for the manufacturers of the DP.

**Table 24. Manufacturers**

<b>Name/Address/Registration Number</b>	<b>Contact</b>	<b>Responsibilities/ Unit Operations</b>
Neurotech Pharmaceuticals, Inc. 900 Highland Corporate Drive Building 1 Suite 101 Cumberland, RI 02864 DUNS: 117685116 FEI: 3012545799	Jacob Patterson, VP Quality Phone: (b) (4) Fax: (b) (4) Email: j.patterson@neurotechusa.com	Manufacturing of DP including packaging and labeling

(b) (4)

(b) (4)

### 3.2.P.3.2 Batch Formula

*Reviewed by CP*

The dosage form of ENCELTO is one implant. The batch formula is included in Table 25, “ENCELTO batch formula components”, provided below.

**Table 25. ENCELTO batch formula components**

(b) (4)

(b) (4)

**Overall Reviewer's Assessment (CP):** An information request was sent on February 10, 2025, asking the Applicant to provide clarifications related to the justification for the (b) (4). The response was received in Amendment 87 (dated February 13, 2025). The Applicant clarified that the (b) (4) was based on the (b) (4) PPQ runs. The information provided is acceptable. The information provided in 3.2.P.3.1 and 3.2.P.3.2 of the original BLA and amendment 87 is sufficient to support the (b) (4) for the purpose of the BLA.


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

#### *Reviewed by CP*

The manufacturing process of ENCELTO is a continuous process (with no intermediate hold steps) from DS formulation to DP packaging and labeling. ENCELTO is manufactured at Neurotech Pharmaceutical, Inc.'s facility (Cumberland, RI) in accordance with CGMP regulations. The DS is (b) (4) to obtain the DP using a semi-automated manufacturing process under an ISO (b) (4) environment. The ISO (b) (4) unit is located and operated in the ISO (b) (4), which is located within an access-controlled modular cleanroom. The DP manufacturing process includes the following (b) (4) steps and (b) (4) operators:

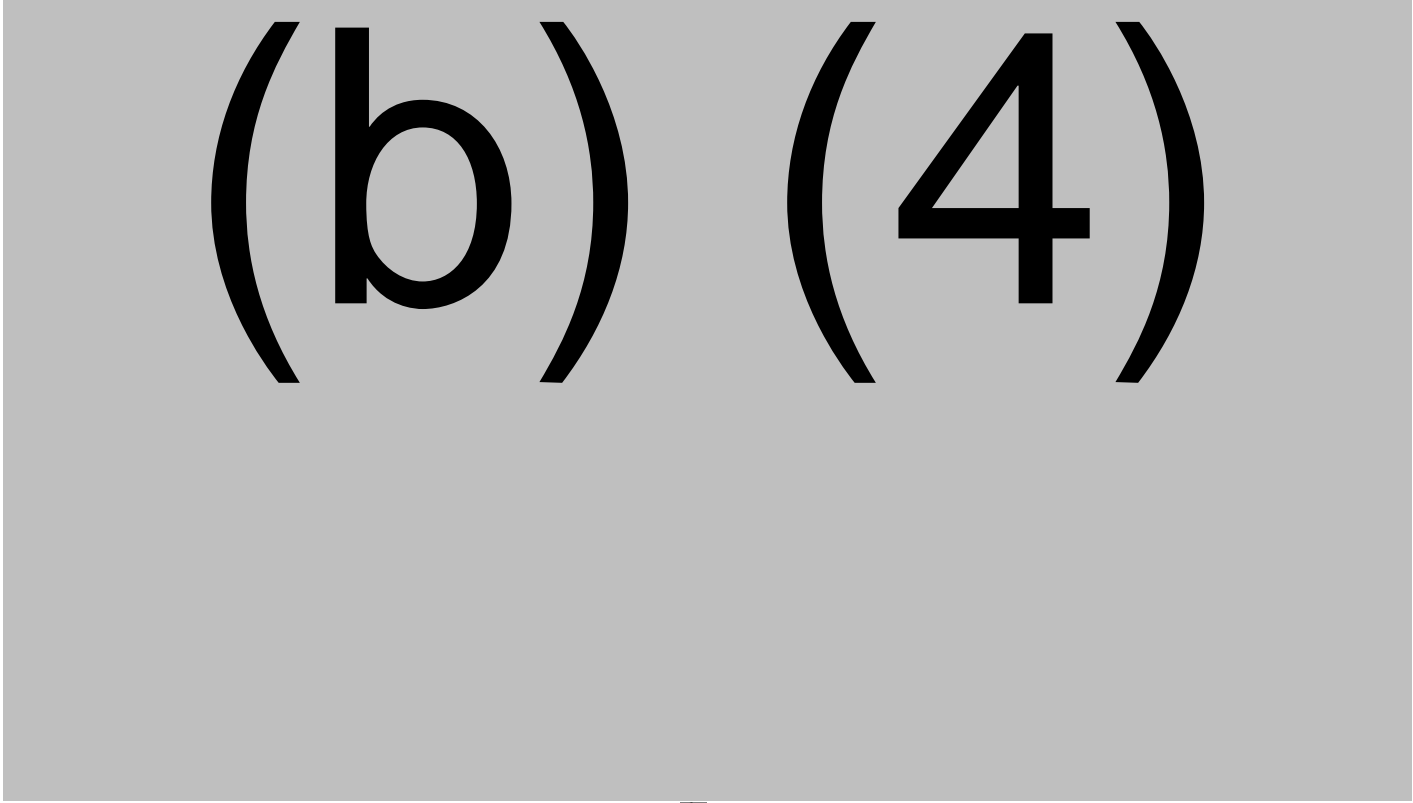
(b) (4)

(b) (4)

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**Table 26. Diagram of the DP manufacturing process**


(b) (4)

A large rectangular area of the document is redacted with a solid gray fill. This redaction covers the entire content area of Table 26, obscuring the diagram of the DP manufacturing process.

ENCELTO is labeled with QA approved and reconciled labels. NT-501 are transferred to Quality for storage in environmental chamber(s) at 37°C (b) (4)

The manufacturing steps and related equipment are detailed below.

(b) (4)

A rectangular area of the document is redacted with a solid gray fill. This redaction covers the manufacturing steps and related equipment details mentioned in the preceding sentence.

14 pages determined to be not releasable: (b)(4)



(b) (4)

### 3.2.P.4.5 Excipients of Human or Animal Origin

*Reviewed by SM*

Endothelial-Serum Free Medium (Endo-SFM) is used in the (b) (4) NT-501 Drug Product (DP) hold medium. (b) (4)

(refer to Section 3.2.S.2.3 for further details). The Endo-SFM contains (b) (4)

**Reviewer's Assessment (SM):** *The excipients of human and animal origin were reviewed and found to be adequate.*

### 3.2.P.4.6 Novel Excipient

*Reviewed by CP and SM*

Endo-SFM is the only novel excipient that is used as i) (b) (4)

as an excipient serving as the hold medium to maintain the DP in the final product packaging throughout the entire shelf life or until point of use.

Endo-SFM is tested for viruses of human and animal origin appropriately. Please refer to section 3.2.P.4.1 - 3.2.P.4.6 above and section 3.2.A.2 for more details on viral safety data.

**Overall Reviewer's Assessment (CP):** *On 22-AUG-2024, Elizabeth Lessey-Morillon, confirmed the (b) (4)*

*provided in the original submission was not sufficient to determine the identity and safety testing of the Endo-SFM for the purpose of the BLA. Two (2) information requests were sent (dated September 12 and 19, 2024) asking the Applicant to provide more detail on the raw materials, including Endo-SFM, used in the manufacturing of the DP. The issue related to identity testing was also discussed during the late cycle meeting (LCM) held October 7, 2024. The response received in Amendments 37 (dated September 19, 2024), 54 (dated October 23, 2024) and 70 (dated December 11, 2024) included the rationale and the*

validation/qualification (where applicable) of the type of testing performed. In Amendment 70, Neurotech provided qualification report (RPT-0014) for the (b) (4), used to confirm the identity of Endo-SFM by ensuring (b) (4). The information provided in Amendments 37, 54 and 70 is adequate to resolve the identity and safety issues (illustrated above) raised during the review of the original submission.

### 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)

Reviewed by CP

The lot release specifications for the DP are provided in Table 34 below.

**Table 35. DP lot release specifications**

Attributes/ Parameters	Test	Method	Acceptance criteria (clinical/process validation)
<b>Quality</b>	Appearance	Visual	<u>Physical State</u> : Implant, solid; Hold Medium, liquid and may contain particles (generally described as fiber, solid, white, or metallic in appearance). <u>Color</u> : Implant, white/off-white; Hold Medium, orange - pink. <u>Clarity</u> : Implant, opaque; Hold Medium, clear.
	Viability	(b) (4)	(b) (4) Viability (b) (4)
	rhCNTF	(b) (4)	(b) (4)
	pH	(b) (4)	(b) (4)
<b>Safety</b>	Sterility	(b) (4)	Implant: No growth Hold Medium: No growth
	Endotoxin	(b) (4)	Implant: (b) (4) Hold Medium: (b) (4)
	Mycoplasma	(b) (4)	Negative
<b>Potency</b>	(b) (4)	(b) (4)	(b) (4) relative potency
<b>Identity</b>	rhCNTF	(b) (4)	Consistent with reference material
<b>Strength</b>	(b) (4)	(b) (4)	200,000-440,000 cells/NT-501

**Reviewer's comment (CP):** An information request was sent on August 9, 2024, asking the Applicant to provide endotoxin specification in EU/Kg of body weight (BW)/hour considering all components present in the final DP (e.g., implant, hold medium) and the lowest body weight in the intended use population. Neurotech provided a response in Amendment 26 (dated August 19, 2024) clarifying that endotoxin testing of the implant and the medium are conducted separately. The hold medium is not administered to the patient, except for residual amount left of the implant after removal from the primary container closure. (b) (4)

The Applicant also provided the conversion of the of the unit from EU/implant to EU/BW, considering the lowest body weight in the intended use population (47.8 Kg from literature search). Because the DP is only administered once in a lifetime in each eye, the calculation provided was as follows: (b) (4)

. The Applicant also asked for the endotoxin specification to be expressed in EU/device as originally provided (b) (4) /Implant and (b) (4) /mL for the hold medium (Endo-SFM). The information provided is acceptable. In the same IR dated August 9 (with clarification sent by FDA via email August 12), the Applicant was asked to specify where in the submission the suitability of the sampling plan for in-process testing of the DS and release of the DP was located in the BLA. The Applicant was also asked to specify the following: volume of the samples, duration of contact with the DS or DP, material composition and size of the consumables used for each test and any information to support the sampling used (e.g., spike/recovery studies when applicable). The response was received in Amendment 26 (dated August 19, 2024). In the response the Applicant provided and updated SOP-2189.07, "Sample Plan for Commercial Manufacturing Process of NT-501, that included the information requested.

The justifications for DP specifications are provided in Table 35 below.

**Table 36. Justifications for DP (ENCERTO) specifications**

Parameter	Test Method	Test Method Number	Acceptance Criteria	Justification
Quality	Appearance	(b) (4)	Physical State: ENCERTO is solid capsule with metallic loop on one end and cap on the other end, Hold medium is Liquid and may contain visible particles	ENCERTO shape of a capsule confirms no gross issues with the membrane. Damaged ENCERTO may impact cell proliferation during shelf life. The hold medium is liquid, which may contain visible particles. The rinse of the

				ENCELTO prior to implantation into patient reduces the risk of transferring particles from the Hold Medium onto the patient.
			Color: ENCELTO is white/off-white, Hold Medium is orange to pink	The color indicator in the hold medium must be within the specified range to ensure that the media is within the acceptable pH range for ENCELTO. This ensures that the encapsulated cells maintain viability during the shelf-life of the ENCELTO.
			Clarity: NT-501 is opaque, Hold Medium is clear	Turbidity of the hold medium indicates a change in the general quality of the product it also indicates possible microbial contamination and a breach in the aseptic process that would cause rejection of ENCELTO.
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	pH	(b) (4)	(b) (4)	(b) (4)

				(b) (4)
	(b) (4)	(b) (4)	(b) (4)	(b) (4)
			(b) (4)	
Safety	Sterility, (b) (4)	(b) (4)	ENCELTO: No growth	Sterility testing with no growth is to ensure the product is free from microbial contamination and has been aseptically processes
	Sterility, (b) (4)		Hold medium: No growth	
	Bacterial Endotoxin, (b) (4)	(b) (4)	ENCELTO: (b) (4) /ENCELTO	This specification is to ensure low level of Endotoxin in ENCELTO and Hold Medium for patient safety as per (b) (4) requirement.
	Bacterial Endotoxin, (b) (4)		Hold Medium: (b) (4)	
	Mycoplasma	(b) (4)	Negative	The specification is based on (b) (4) requirement to have no mycoplasma in final product.
Potency	(b) (4)	(b) (4)	(b) (4) Relative Potency Stability: (b) (4) Relative Potency	The specification range is based on (b) (4) performance of ENCELTO tested in accordance with standard operating procedures at (b) (4)

				(b) (4)
Identity	(b) (4)	(b) (4)	(b) (4)	The identity specification of the ENCELTO is based on (b) (4)
Strength	(b) (4)	(b) (4)	Internal Release: 200,000-440,000 cells/ ENCELTO Stability: (b) (4) cells/ NT-501	The specification range for cell number is based on (b) (4) of cells observed in ENCELTO tested in accordance with test method at (b) (4). The specification is based on manufacturing data (b) (4)

**Overall Reviewer's Assessment (CP):** An information request was sent on February 10, 2025, asking the Applicant to clarify the timing of the sampling for sterility, endotoxin and appearance release test and to confirm that the proposed sampling was validated with PPQ runs. The response was received in Amendment 87 (dated February 13, 2025). The Applicant clarified that sterility and endotoxin testing occurs between day (b) (4) and day (b) (4) and that appearance testing occurs up to (b) (4) as it is performed before the other release tests. The Applicant updated the sampling plan (SOP-2189) in section 3.2.P.5.1 of the BLA to reflect this clarification.

The information provided in the original submission and Amendments 26 (dated August 19, 2024) and Amendment 87 (dated February 13, 2025) is acceptable to support the specifications established for ENCELTO.

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

Reviewed by CP

All non-compendial analytical procedures were validated in accordance with FDA's Guidance for Industry: "Analytical Procedures and Methods Validation for Drugs and Biologics (July 2015)" which follows ICH Q2(R1) guidelines.

All compendial analytical procedures, including compendial microbiological testing (sterility and bacterial endotoxin), were qualified according to current United States Pharmacopoeia (USP) requirements.

The analytical method protocols and reports used for validation/qualification are listed in Table 36 below.

**Table 37. Analytical Methods Protocols and Reports**

Test Method	Test Method Number	Validation Protocol Number	Validation Report Number
Appearance	(b) (4)	(4)	(b) (4)
Sterility, (b) (4)			
Bacterial Endotoxins Test, (b) (4)			
(b) (4)			
(b) (4)			
(b) (4) (cell number)			
Viability (b) (4)			
Identity Assay (b) (4)			
Mycoplasma, (b) (4)			
pH, (b) (4)			


(b) (4)

#### Appearance

The appearance test is performed by (b) (4)

(b) (4)

(b) (4)



**Table 38. Summary results of the validation of the appearance test**

Parameter	Acceptance Criteria	Results	Pass/Fail
<div>(b) (4)</div>			





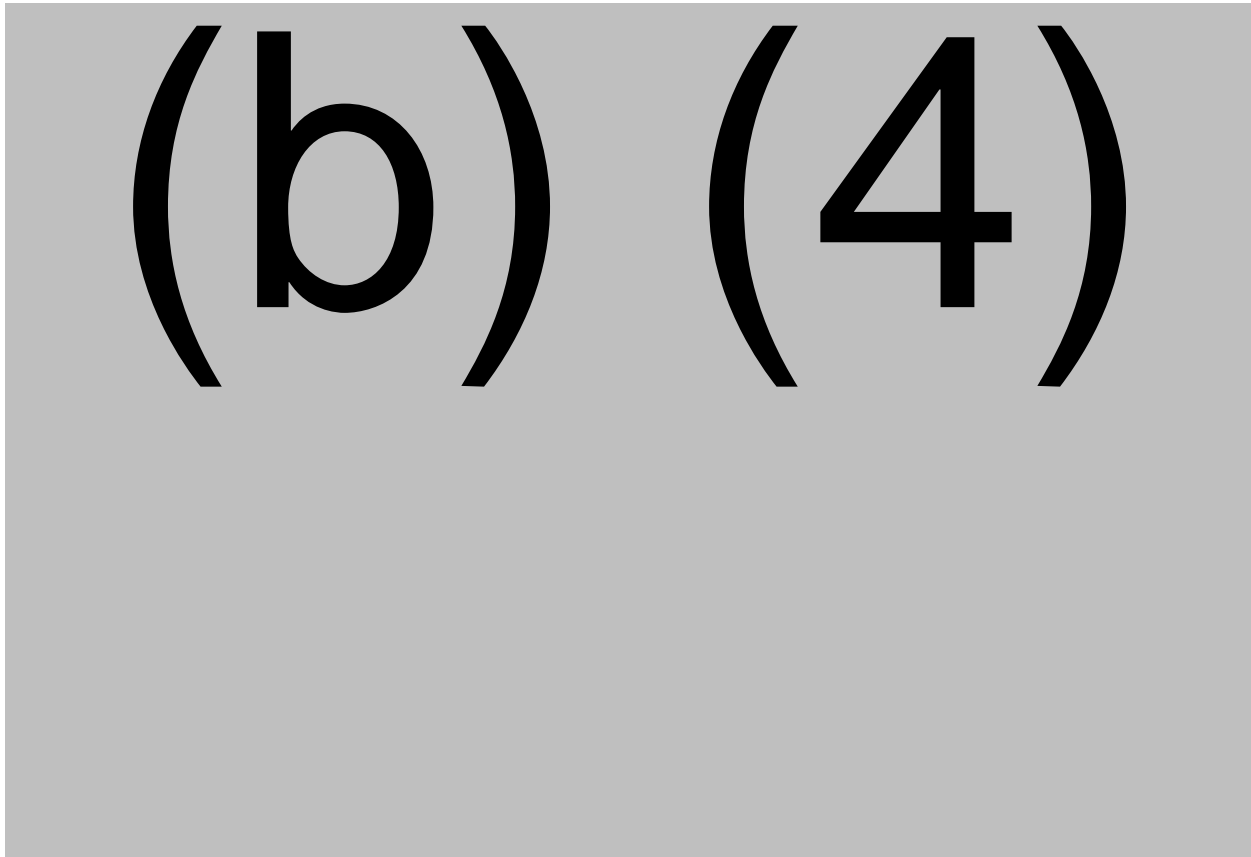
Sterility Testing (b) (4)

The sterility testing qualification of the DP was performed per Neurotech (b) (4)



The summary results for the validation of the sterility test are provided in the tables below.

**Table 42. summary results for the validation of the sterility test DP**



(b) (4)

(b) (4)

(b) (4)

(b) (4)

Endotoxin (b) (4)

The bacterial endotoxins test for DP is performed per (b) (4)

Please refer to the tables below for the summary results of the qualification of the endotoxin test.



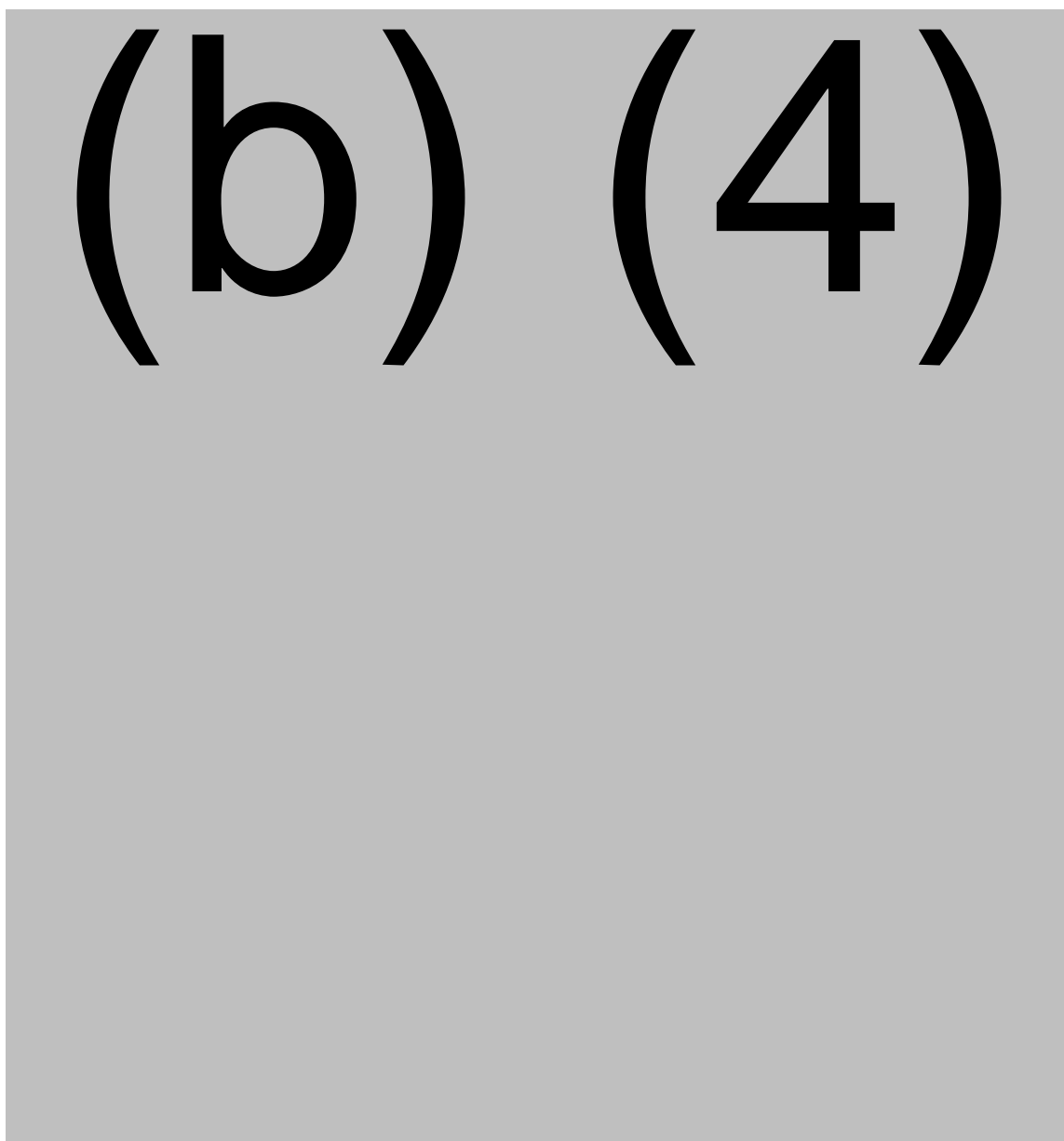
**Overall Reviewer's Assessment (CP):** The information provided in sections 3.2.P.5.2 and 3.2.P.5.3 is acceptable.

### 3.2.P.5.4 Batch Analyses

*Reviewed by CP*

The batch analysis test results presented in this section include data from DP batches manufactured as process performance qualification (PPQ) batches under PPQP-V448 ("Process Performance Qualification Protocol for Manufacturing Process of Neurotech ECT Product NT-501 Using (b) (4) ).

**Table 53. PPQ Batches analysis test results**



(b) (4)

### 3.2.P.5.5 Characterization of Impurities

#### *Reviewed by CP*

The potential risk of contamination by (b) (4) was evaluated and provided in risk report (RA-0144). The risk assessment covers all major areas of DP manufacturing processes, including DS, PAC, and the DP manufacturing (b) (4) and storage. The materials, reagents, and conditions during each manufacturing process were evaluated for the likelihood of contamination by (b) (4) if both were present.

According to the Applicant, the evaluation of the (b) (4) risk that was included in the (b) (4) evaluation (discussed in section 3.2.P.2.6) resulted in a determination of (b) (4) manufacturing process, including the storage and shelf-life of the DP. Please refer to section 3.2.S.3.2 for additional information of the assessment of impurities (e.g., (b) (4) ) in the final (b) (4) .

**Overall Reviewer's Assessment (CP):** The information provided in section 3.2.P.5.4 and 3.2.P.5.5 is sufficient to support that the release testing ensures the safety and quality of the DP.

### 3.2.P.6 Reference Standards or Materials

*Reviewed by SM*

In-house-prepared reference materials as well as commercially available reference standards used for release and stability testing of NT-501 are listed in Table 53.

**Table 54. In-house and Commercially Available Reference Standards and Materials Used for NT-501 Testing**

Category	Material Description	Tests Applied	Manufacturer/Supplier	Part/Lot Number
In-house- prepared reference material	(b)	(4)	(4)	(4)
Commercially Available Reference Standard				

(b) (4)

The NT-501 reference material used throughout product development and commercialization is the (b) (4)

routine and stability testing of NT-501 as shown in Table 1 above. The details of the NT-501 reference materials used throughout the development of NT-501 are listed in Table 54.

**Table 55. NT-501 Reference Material Lots Used Through NT-501 Development**

(b) (4)			
---------	--	--	--

The Lot (b) (4) of NT-501 reference material has been used to support NT-501 release testing and stability studies throughout product development and clinical studies. Lot (b) (4) is the first NT-501 reference material characterized and qualified using the methods as listed in Table 55 to compare to (b) (4) obtained from (b) (4). The results are shown in Table 55.

**Table 56. Characterization of NT-501 Reference Material Lot (b) (4)**

Test	Test Method Category	Acceptance Criteria	Result
(b) (4)			



(b) (4)

N/A: Not applicable

The in-house NT-501 reference material Lot (b) (4) was prepared from (b) (4)

Lot (b) (4) was used as the (b) (4) assay control during phase 3 clinical studies with Lot (b) (4) used as the NT-501 reference material for lot release testing and stability studies. Initial characterization for identity of lot (b) (4) was by (b) (4) (b) (4).

**Table 57. Initial Characterization of the Current NT-501 Reference Material Lot (b) (4)**

Test	Test Method Category	Acceptance Criteria	Result
(b) (4)			

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

(b) (4)

Future new in-house NT-501 reference material will be prepared following the method used to prepare NT-501 Reference Material Lot (b) (4). Qualification testing of the new NT-501 reference material will be performed per the approved tests and acceptance criteria. To ensure continuity in product quality attributes for the reference material, such as quantity and potency, the new NT-501 reference material will be tested for critical quality attributes - (b) (4). For the (b) (4) reported results will be generated with the new NT-501 material as sample. The bias between the current and new reference will be evaluated to determine if a new value needs to be assigned to the new reference. A value assignment will be performed by adjustment of the (b) (4) value to the observed bias as input for the (b) (4)

**Table 59. Summary of Proposed Release and Characterization Testing for Future NT-501 Reference Material**

Test	Test Method	Acceptance Criteria
(b) (4)		

(b) (4)

The stability of the new NT-501 reference material will be assessed by statistical assessment of the (b) (4) assay control data (b) (4) to determine expiry re-evaluation extension. An initial expiry re-evaluation date of (b) (4) is assigned based on historical experience of prior NT-501 reference materials' stability at (b) (4) (Refer to Historical Trending of Biological Potency section of (b) (4) for supporting stability data). Note that the (b) (4) assay control is a (b) (4) that is prepared the same as the reference material, that is expected to meet the same criteria, and that is a different lot from the NT-501 reference material lot.

Commercial Reference Standards used for NT-501 Testing





Table 59 lists the commercial reference standards, the source of the materials, and the method in which the material is used. Neurotech certifies all incoming new lots of commercially available reference standards by testing using the respective methods prior to use for release and stability testing.

**Table 60. Commercially Available Reference Standards Used in NT-501 (b) (4)**

Category	Material Description	Manufacturer/ Supplier	Catalog Number	Test Method/ Where Used
Commercially Available Reference Standards	(b) (4)			

(b) (4)

(b) (4)



**Overall Reviewer's assessment (SM):** *The qualification of the in-house and commercially available reference standards and materials used for release and stability testing of ENCELTO discussed above was reviewed and found acceptable. Please also refer to section 3.2.S.5, Reference Standards or Materials, for additional information on DS reference material.*

### **3.2.P.7 Container Closure System**

*Reviewed by SM*

Please refer to section 3.2.P.2.4 (Container Closure System) for overview of the Container Closure System (CCS).

Table 61 below provides a list of primary/inner container closure components and material of construction. Components are received non-sterile from the supplier into Neurotech's Quality Materials Management program prior to Quality release to manufacturing for packaging and shipment to (b) (4) for sterilization (refer to Section 3.2.A.1 for (b) (4) sterilization). Refer to Section 3.2.P.2.6 for compatibility testing performed.

**Reviewer's Comment (SM):** During the review of the BLA submission (Amendment 53, dated October 3, 2024), the 'Primary Package' was changed to 'Inner Container' and the 'Secondary Package' was changed to 'Outer Container'. Based on the new designation, the inner and outer container constitutes the Primary Container Closure.

Table 61. NT-501 Inner Container Components Component	Supplier	Material of Construction	Compliance Reference Documents <sup>b</sup>
Inner Container <sup>a</sup>	(b) (4)		
Luer Lock Cap <sup>a</sup>			
Inner Container Lid Film			

<sup>a</sup> (b) (4)

PET = polyethylene terephthalate

The dimensions of the CCS components are shown in below figures 21 - 24.

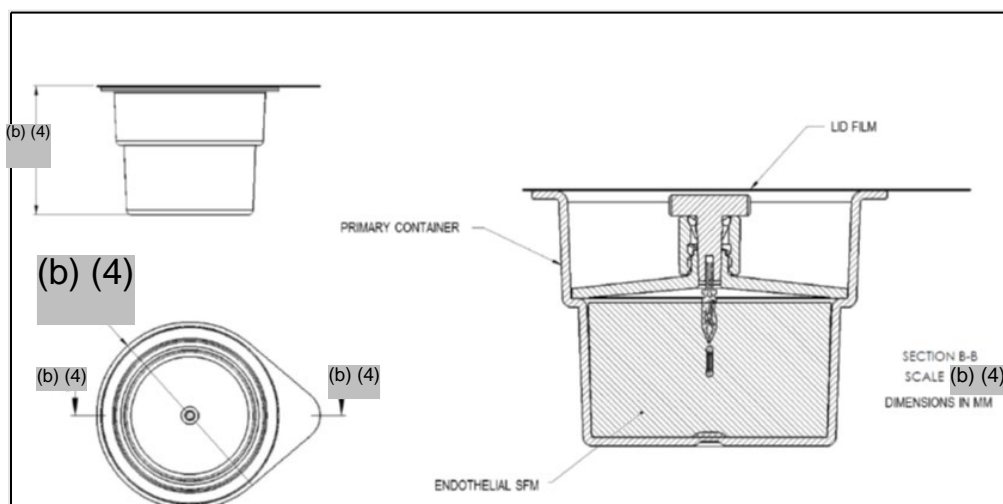


Figure 21. Inner Container Inclusive of Luer Lock Cap and Suspended NT-501

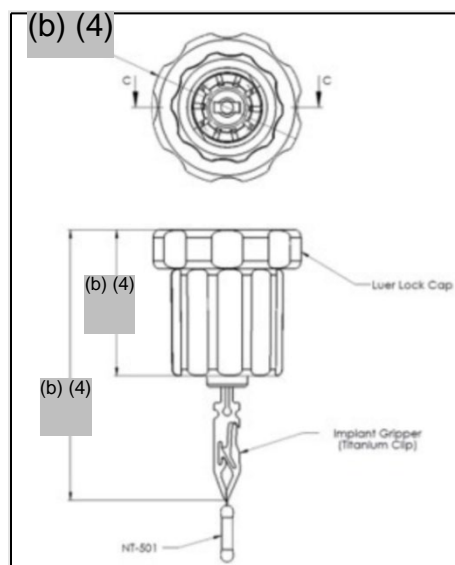
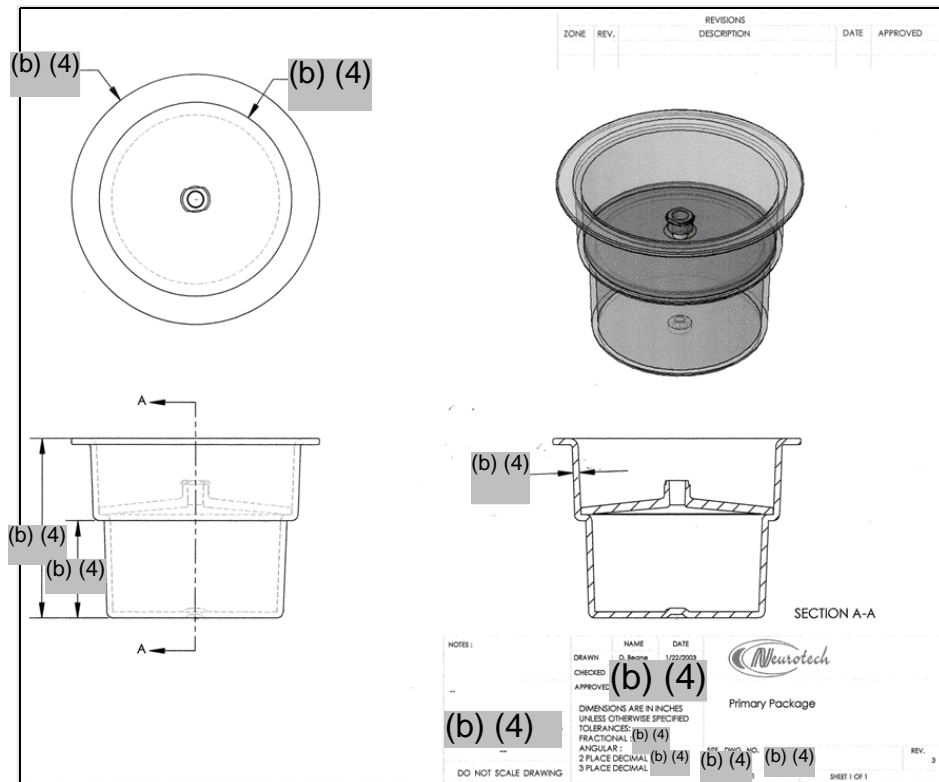


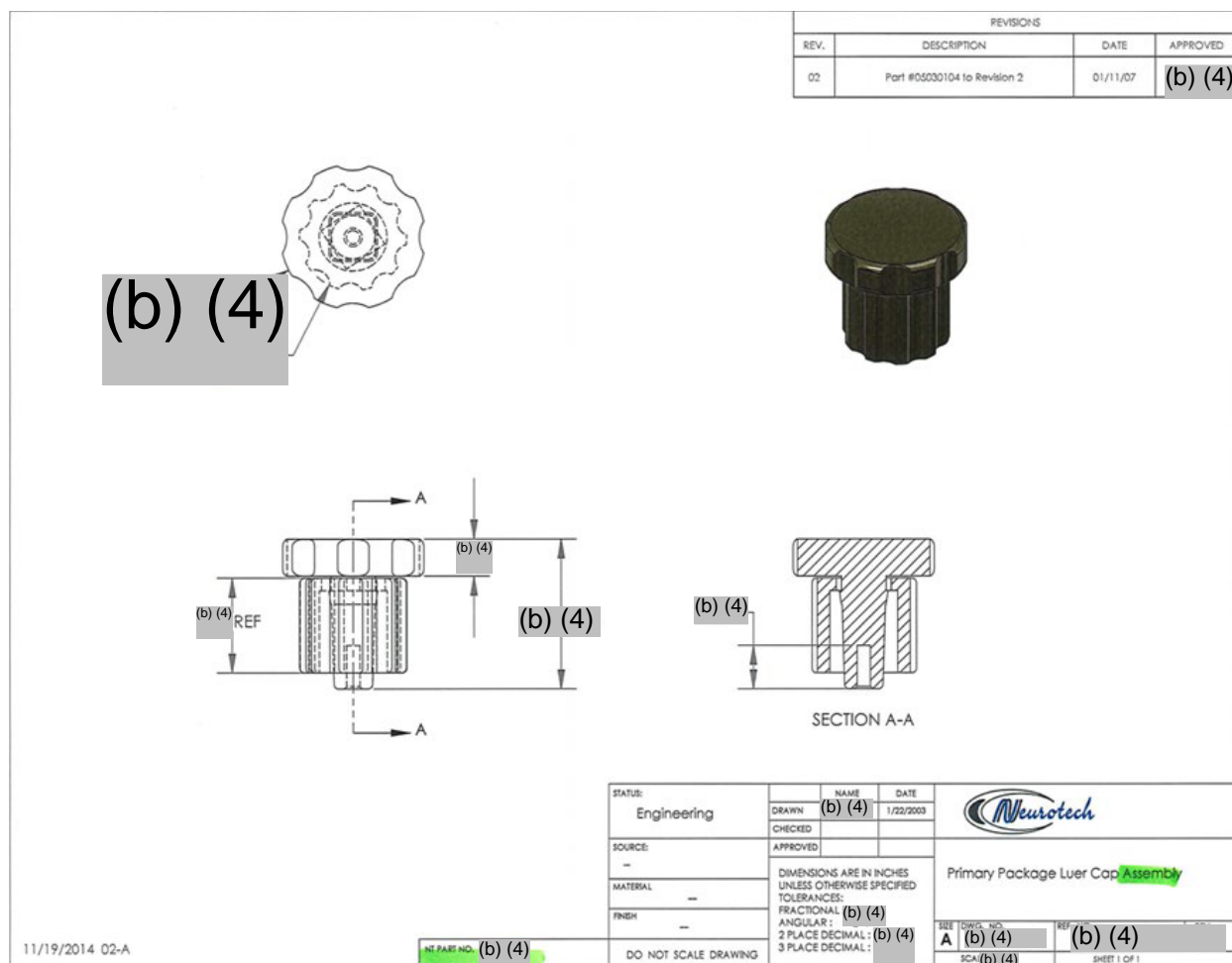
Figure 22. Luer Lock Cap, Titanium Clip, and NT-501



**Figure 23. Inner Container Drawing with Size Measurements**

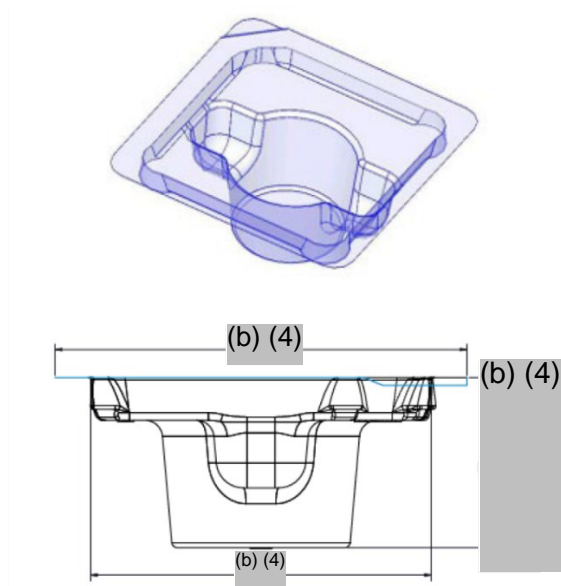
A copy of the Certificate of Compliance (COC) for the Primary Package Assembly in Trays (from (b) (4)) was submitted and was found adequate. A copy of the Certificate of Compliance (COC) for the Primary Package Luer Cap Assembly (from (b) (4)) was submitted and was found adequate. Please refer to Figure 24 below for the drawing of the Luer Cap.





**Figure 24. Inner Container Luer Cap Assembly Drawing with Size Measurements**

The outer (b) (4) package is shown in Figure 25 below. It is the NT-501 Final Product Package container closure integrity protection during the NT-501 shelf-life period, shipping period, and surgical preparation. Table 54 provides a list of components and material construction of outer container of the container closure.



**Figure 25. NT-501 Outer Container of the Primary Package**

**Table 62. NT-501 Outer Container Components**

Component	Supplier	Material of Construction	Compliance Reference Documents <sup>a</sup>
Outer Container	(b) (4)	(b) (4)	(4)
Outer Container Lid Film			

a Drawing title nomenclature is carried over from historical development nomenclature, note secondary package is equivalent and now represents the outer container of the NT-501 Final Product Primary Package CCS.

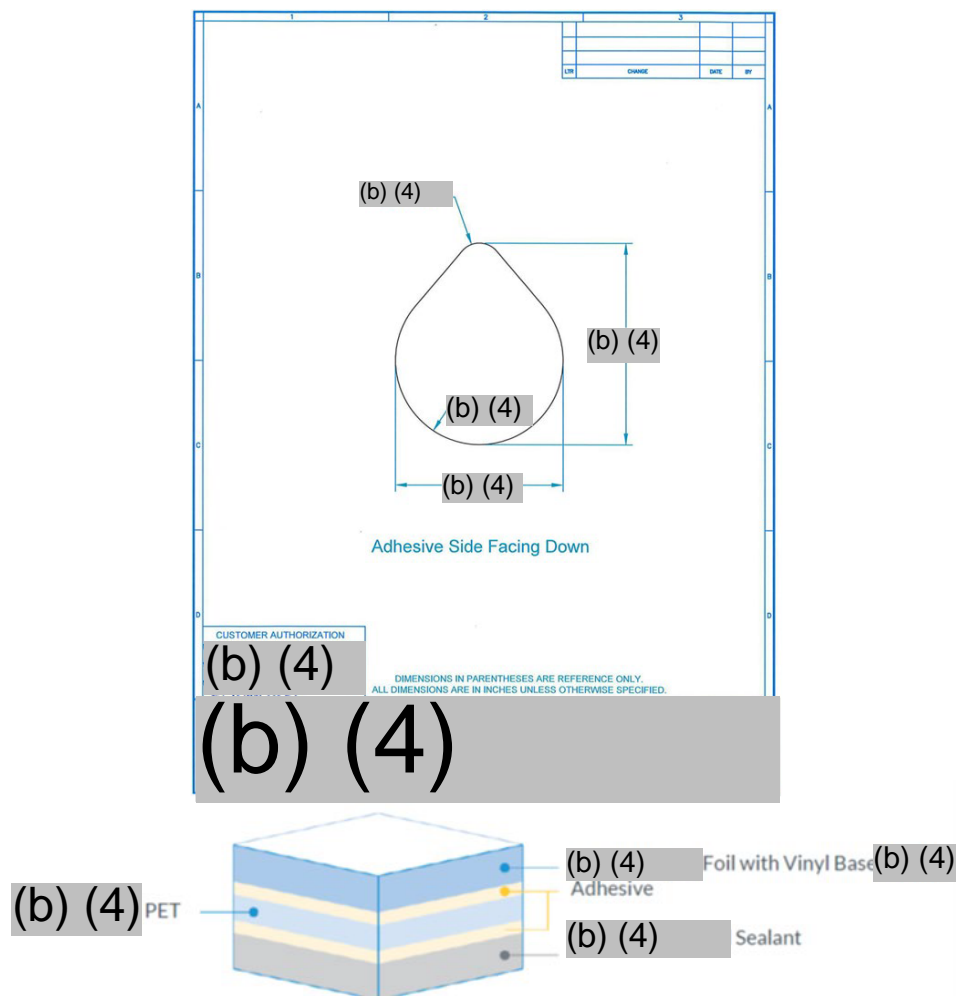
CoC= Certificate of compliance; (b) (4)

PET= polyethylene terephthalate

#### Inner and Outer Container Lid

Labeling was provided for the high barrier, flexible packaging lamination used as the inner and outer container lid, (b) (4) also marketed as (b) (4). A copy of the

Certificate of Compliance (COC) for the primary package lid was reviewed and found adequate. Refer below to the drawing of the primary package lid (Figure 26).



**Figure 26. Drawing of the Inner Container Lid.** (b) (4) is equal to (b) (4) .

(b) (4) is a medical-grade lidding material known for use in pharmaceutical, personal care products, or medical device packaging. The foil/film construction provides good puncture, water resistance, and has a wide seal temperature range. It has excellent moisture, oxygen, and UV barrier characteristics. It is compatible with (b) (4) sterilization, seals to most rigid packaging materials and shown to be noncytotoxic (for further information related to the stability and compatibility of the lid is in section 3.2.P.2.4 and the DMPQ memo ). A representative Certificate of Irradiation (Col) for sterilization certificate was reviewed and found to be adequate.

There are three closures associated with the final product packaging container closure system:

- A Luer lock cap closure that seals the lower compartment of the inner container (which contains the NT-501 and Endo-SFM Hold Medium) (Figure 8, section 3.2.P.2.4)
- A (b) (4) seal, gas-impermeable lid film that seals the inner container (Figure 8, section 3.2.P.2.4)
- A (b) (4) seal, gas-impermeable lid film that hermetically seals the outer container (Figure 9, section 3.2.P.2.4).

The (b) (4) seal method for lid film application of both the inner and outer container are controlled by semi-automated (b) (4)-sealing equipment that regulates seal (b) (4) (refer to Section 3.2.P.3.3).

Potential extractable/leachable impurities stemming from the container closure system, are discussed in Section 3.2.P.2.6 and Section 3.2.R.3. To comply with quality requirements per ICH Q8(R2), the capability of the Final Product Packaging to maintain sterility of NT-501 was confirmed by sterility testing lot release, per Section 3.2.P.5.1. The study R576A supports a (b) (4)-week shelf-life (refer to Section 3.2.P.2.5.4 for the results of the testing of PPQ DP lots).

### Packaging and Labeling

Neurotech uses two labels, one for the outer container and a separate one for the package/carton (b) (4) Corepack). The container label (provided in Section 1.14.1.1) was reviewed and found to be adequate, which is attached to outer container of NT-501 on the day of encapsulation and prior to placement into shelf-life long-term storage (shelf life/expiry date). A separate package/carton label (provided in Section 1.14.1.1) was reviewed and found to be adequate. The carton label is applied by third party logistics firm (b) (4) at the time of just-in-time pack out for shipment to support surgical schedules. This label includes the 'use by date' which is inclusive of the labeled secondary packaging box at 16-37°C for up to (b) (4) days from the time of pack out. The NT-501 "use by date" cannot exceed the "shelf-life expiry date." Note that the package/carton label will be used as the primary display panel (PDP). (Note: The NT-501 Instructions for Use provides a comprehensive overview of the product user interface, storage and handling, warnings, precautions, contraindications, and operational sequence for the NT-501 Implant/Explant procedure.)

### NT-501 Final Product Package Labeling at Neurotech

Neurotech applies the NT-501 final product package label to the outside of each outer container on the sealed lid. Each labeled NT-501 Final Product Package is then (b) (4) Quality Assurance for storage in (b) (4) while awaiting lot release. Once pre-defined specifications are met, the labeled NT-501 Final product package is shipped in (b) (4)

### Shipping and Distribution

Shipping activities occur from Neurotech's cGMP facility (Cumberland, RI) (b) (4)

(b) (4) [REDACTED] and  
then from the commercial distributor to the surgical site.

Shipping from Neurotech to Distributor

(b) (4) [REDACTED]

Shipping Validation from Neurotech to Distributor

(b) (4) [REDACTED]

NT-501 Pack-Out labeling and Shipment from Distributor to Surgical Site

(b) (4) [REDACTED]

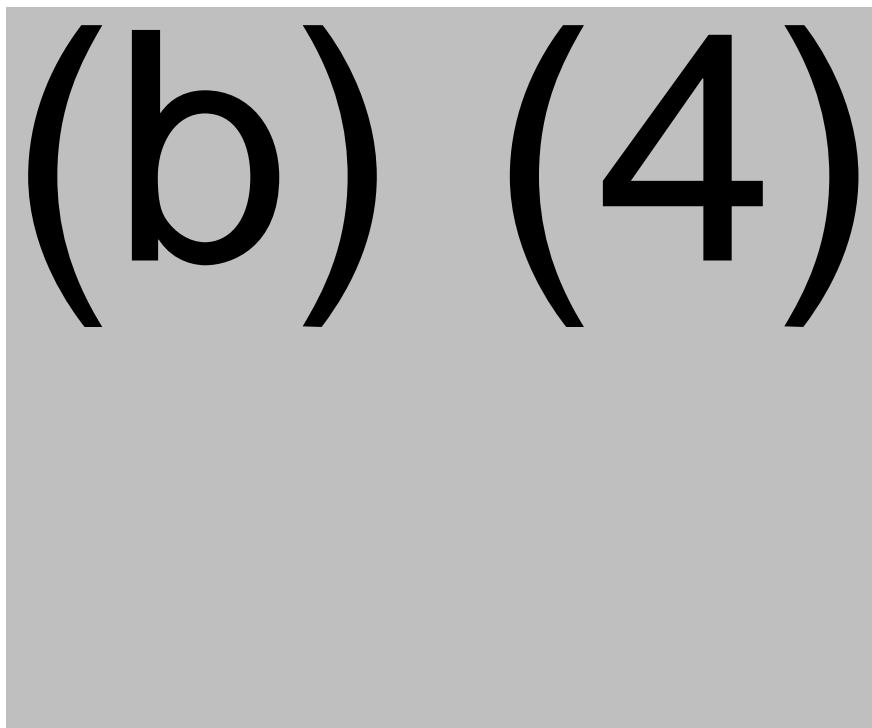


Figure 21. NT-501 Shipping System (b) (4) shipper system)



Figure 22. (b) (4) Corepack Carton showing Label Placement

#### Shipping Validation Studies from Distributor to Surgical Site

Validation of the NT-501 custom pack-out shipping system was conducted by an external contract laboratory (b) (4) to demonstrate the stability of NT-501 at the transport conditions of 16-37°C for (b) (4) days. In this study, the (b) (4) in accordance with the guidelines of the (b) (4) ) for testing (b) (4) packaging (Study P0235). The (b) (4) -day duration simulates the worst-case scenario and allows for wait time at the sites of use following shipment receiving.

Applicant submitted a (b) (4) qualification report 'T18-00636' for qualification of the (b) (4) Insulated Shipping Container - (b) (4)

The distribution qualification and validation report '18-00636' describes the results for (b) (4) distribution testing, through controlled (b) (4)

This testing demonstrated that the packaging configuration can maintain the product in satisfactory condition after exposure to transportation forces encountered during this testing. Review of the test results indicate that the maximum load packing configuration and product-maintained integrity throughout distribution testing.

Applicant submitted the (b) (4) qualification and distribution validation of (b) (4) shipping container report 'p0235' to validate the (b) (4) shipping container used for transportation of the final clinical drug product NT-501 to support the BLA submission approval. Following (b) (4) testing and inspection of the (b) (4) shipping container and tertiary packaging, the final product was visually inspected, and the product performance was analyzed for (b) (4) viability (b) (4), potency (b) (4) and cell number (b) (4). The total duration of shipment exposure for the NT-501 product contained within the (b) (4) shipper was (b) (4) from time of initial packaging and shipment to (b) (4) followed by return to Neurotech for product testing. Based on the results of (b) (4) testing and distribution testing performed by (b) (4), and post-testing analysis of NT-501 drug product, the (b) (4) shipping container and tertiary packaging met the (b) (4) distribution standards for physical integrity, the product label on NT-501 packaging remained adhered, intact and legible, the NT-501 drug product within E38NT shipping configuration maintained primary and secondary packaging seal integrity, sterility, (b) (4) output, (b) (4) potency, and viability, under (b) (4) temperatures for up to (b) (4) including exposure to (b) (4) testing conditions. This study supports the shipping / distribution time of (b) (4) days in the (b) (4) shipping container.

The Applicant submitted a developmental study 'r444-2 – NT-S01-6A.02 for the evaluation of drug product distribution extension and in vivo performance. This study compared the performance of expired and non-expired (control) NT-501.6A.02 final drug product following exposure to (b) (4) simulated transit period. This study was designed to understand how final product subjected to an extreme drug product distribution scenario (b) (4)

(b) (4)

perform relative to controls (non-expired drug product held (b) (4)

. According to the Applicant, this study will also help justify the release specification for (b) (4) output range, examine the potential for extending drug product distribution time, and set parameters on allowable shipping / distribution temperature during distribution of the drug product in a commercial setting. The study product performance was evaluated (b) (4)

Rabbits. After the (b) (4) simulated transit period, all final products were evaluated for (b) (4) output, after which the final products were selected for implant. (b) (4) final products with extremes in (b) (4) output (final products with high and low (b) (4) output) were chosen for implantation from the groups - control 37°C, expired 37°C, expired 16°C, expired (b) (4). The final products that were not implanted into rabbits were assessed for cell viability, cell number and histology. The (b) (4) output from (b) (4) final products was compared to the (b) (4) output from the intraocular implant. The conclusions drawn from the study results are:

1. The results suggest a single consistent dose of (b) (4) is produced by the intraocular implanted NT-501 product when implanted in the (b) (4) rabbits irrespective of (b) (4) output from NT-501 product (b) (4).
2. Product with extended shelf life of up to (b) (4)-week expiry and transit times of weeks exposed to temperatures between (b) (4) and 37°C performed statistically equivalent to control devices when implanted in (b) (4) rabbits, suggesting that drug product remains functional and safe over an extended distribution period.

#### Conclusions to Justify (b) (4)-Day Shipment Duration

Neurotech has designed and evaluated a shipping container (b) (4) shipper system) that can transport NT-501 under extreme conditions for a period of up to (b) (4) days which allows the product to be shipped anywhere in the world. Once on site, NT-501 can be stored within the corepack up to the use-by-date as shown on carton label. In addition, real-time continuous Tempale 4 USB (b) (4) will continue to be utilized and results recorded for each shipment of NT-501 prior to each surgery to ensure the NT-501 will remain within the established temperature range of 16-37°C during the (b) (4)-day transit period.

**Reviewer's comment (SM):** *The transit studies related to stability are included under section 3.2.P.8.*

**Overall Reviewer's Assessment (SM):** *The CCS including the packaging and (b) (4) shipping system supports the integrity and stability of the product during long term storage and shipment/transportation from the manufacture site to the storage/distribution site and from the storage/distribution site to the clinical site for (b) (4) weeks at 37C including shipment period of (b) (4) days (b) (4) weeks) at 16-37°C. The reports submitted on studies conducted were reviewed and found to be adequate.*



### 3.2.P.8 Stability

#### 3.2.P.8.1 Stability Summary and Conclusion

##### *Reviewed by SM*

The Applicant submitted (section 3.2.P.8.3) the long-term stability studies of (b) (4) NT-501 PPQ/registration batches - (b) (4) through (b) (4) weeks. The NT-501 PPQ/registration batches' stability data from (b) (4) weeks of stability met all acceptance criteria. Stability studies demonstrated physical, chemical, biological, and microbiological stability of NT-501 through the proposed shelf-life of 12 weeks when stored at the intended long-term storage condition of 37°C (b) (4).

Supportive stability data comes from (b) (4) phase 3 clinical batches which represented the ENCELTO commercial manufacturing process. This clinical batch data, with up to 12 weeks at (b) (4) representative batches) and up to (b) (4) weeks at (b) (4) representative batches), supports the proposed NT-501 stability profile and the 12-week shelf life. The stability data package on all (b) (4) clinical batches is provided in section 3.2.P.2.3 .

The specifications used for evaluation of NT-501 stability are listed in the below table. The stability attributes/parameters listed are the same as for product release. NT-501 lot release and stability samples are assayed for (b) (4) output by (b) (4) Cell number by (b) (4), Potency by (b) (4), Sterility, pH, and Appearance. Two (2) additional assays, container closure integrity (CCI) and product integrity, were performed for stability evaluation. The descriptions of the analytical procedures used for lot release and stability testing of NT-501 are provided in Section 3.2.P.5.2 and the respective analytical method validations are provided in Section 3.2.P.5.3.

**Reviewer's comment (SM):** During the review of the specifications, I noted that the stability acceptance criteria are broader in range for (b) (4), relative potency, viability, (b) (4), compared to that for product release. An information request was sent on October 4, 2024 for a justification for the difference in the two acceptance criteria. In response to the information request, the Applicant indicated that a detailed assessment and data analysis of the stability acceptance criteria are provided in BLA section 3.2.P.5.6.2..

**Table 63. Stability Specifications**

Parameter	Test Method	Test Method Number	Acceptance Criteria
Quality			

Appearance	Visual	(b) (4)	<b>Physical State:</b> NT-501 is solid capsule with metallic loop on one end and cap on the other end; Hold Medium is liquid and may contain visible particles <b>Color:</b> NT-501 is white/off-white; Hold Medium is orange to pink <b>Clarity:</b> NT-501 is opaque, Hold Medium is clear
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Container Closure Integrity	(b) (4)	(b) (4)	Pass
pH	(b) (4)	(b) (4)	(b) (4)
<b>Safety</b>			
Sterility	(b) (4)	(b) (4)	NT-501: No Growth NT-501 Hold Medium: No Growth
<b>Potency</b>			
(b) (4)	(b) (4)	(b) (4)	(b) (4) Relative Potency
<b>Purity</b>			
Viability	(b) (4)	(b) (4)	(b) (4) Viability
			(b) (4)
Product Integrity	(b) (4)	(b) (4)	(b) (4)
<b>Strength</b>			
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Maintenance of product quality during shipping is confirmed as part of the Shipping Validation study and a use-by stability is established based on NT-501 final product package shipping conditions. Please refer to section 3.2.P.7 above for further details.

Two photostability studies (p0272-01-r0272-01 and p0287-02-p0287-02) of the NT-501 drug product were conducted according to ICH (b) (4). The purpose of these studies was to evaluate the photostability of the final product NT-501 to assess the impact of light on product stability. Per normal handling protocol, the NT-501 drug product (DP) is stored for up to 12-weeks at 37°C within a controlled (b) (4). During shipment from the warehouse to the surgical center and then during storage at the surgical

center, the NT-501 is sealed within a tamper resistant, light blocking package and only removed at time of surgical use. The results from the study p0272-01-r0272-01 of testing of light exposed to NT-501 in primary and secondary container-closure indicate that extensive exposure to sunlight results in changes to critical quality attributes. Based on these findings, the Applicant conducted the second photostability study p0287-02-p0287-02, to assess photosensitivity of NT-501 in light blocking packaging (Carton) that is used during shipment and surgical center storage. The photostability testing data collected in this study shows that NT-501 drug product is appropriately protected from light exposure and photostable within the marketing package. The proposed marketing label for the drug product container and the tamper resistant marketing package (carton) include the light storage statement "PROTECT FROM LIGHT".

The results from stability studies have demonstrated constant levels in (b) (4) relative potency and an (b) (4) in viability and (b) (4) in (b) (4) concentration observed over time. The Applicant stated that these observed trends in viability and (b) (4) concentration are aligned with the historical performance observed with phase 3 clinical batches and supported the product's anticipated stability profile. There was no trend observed in pH. The results for sterility, product integrity, and CCI met the shelf-life acceptance criteria. The statistical analysis of stability data did not exhibit deviations from expected historical performance of comparable NT-501 Phase 3 clinical batches. In summary, the NT-501 PPQ/registration studies produced data to support the proposed 12-weeks shelf-life. The drug product transported and stored (16-37°C) in the sealed, final product package with a label statement "PROTECT FROM LIGHT" is photostable.

Based on the study results and above discussion, the proposed shelf-life for NT-501 is 12 weeks from the date of manufacturing (e.g., date of encapsulation) when stored at (b) (4). The proposed shelf life of the product is acceptable.

#### **r576b - NT-501 Product Stability Evaluation of Simulated Distribution (b) (4) 12-Week Expiry:**

This study R576B was conducted to collect (b) (4) week simulated shipping data at (b) (4) and (b) (4) °C for (b) (4) timepoint (b) (4) the 12-week expiry for NT-501 i.e., (b) (4) weeks (b) (4) manufacture. (b) (4) control cohort of NT-501 was stored at 37°C for (b) (4) weeks and (b) (4) simulated shipping test groups of NT-501 were exposed to a (b) (4) week (b) (4) period at (b) (4) storage at 37°C for (b) (4) weeks. The study samples were tested at (b) (4) weeks post manufacture. The sterility testing was performed (b) (4) weeks post manufacture. This study results demonstrated that the NT-501 met the stability acceptance criteria at week (b) (4) for a control and simulated shipment groups exposed to a (b) (4) period at (b) (4) for viability, (b) (4) output, and (b) (4). Additionally, all groups remained below (b) (4) relative to the (b) (4). The conclusion drawn from this study is that NT-501 meets the preset stability acceptance criteria (per F1085D) following a (b) (4) week simulated shipping period (b) (4) the 12-week expiry.

### **r588 - NT-501 Product Stability Evaluation of Simulated Distribution over Shelf-Life:**

The purpose of study R588 was to collect stability data for (b) (4) week simulated shipment periods of NT-501 Final Product at the start and end of the product shelf-life. In this study, the Applicant evaluated (b) (4) separate simulated (b) (4) week shipping periods for the NT-501 final product – at the start of shelf-life (week (b) (4) to week (b) (4) and at the end of shelf-life (week (b) (4) to week 12). The study included (b) (4) control cohort stored at 37°C and (b) (4) simulated shipping test groups exposed to a (b) (4) week (b) (4) period at (b) (4). These samples of NT-501 final product were tested at (b) (4) 12-weeks post manufacture. The results from this study indicate that all samples from each timepoint and study group met the NT-501 stability acceptance criteria for viability, (b) (4) and product integrity (per the document F1085D). The conclusion drawn from this study results is that NT-501 meets stability acceptance criteria following a (b) (4) week simulated shipment period at the start and end of the product shelf life of 12 weeks.

### **3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment**

#### *Reviewed by SM*

The Applicant commits to monitor the results for ongoing stability studies, to continue the long-term stability studies through the proposed shelf life, to initiate and conduct stability studies on the first (b) (4) commercial production batches of NT-501 and (b) (4), thereafter, at least (b) (4) production batch will be added to the stability program. The results of these stability studies will be reported in routine annual reports.

The Applicant commits that in case when significant changes to the manufacturing process or analytical methods for NT-501 are introduced after licensing, stability will be re-evaluated, and updated data will be submitted as a supplement to the BLA. The specifications and stability assessing parameters is as listed in the above section 3.2.P.8.1 in table 3. The long-term stability protocol is shown in Table 56 below.

**Table 64. Stability Protocol: Long-Term (37°C (b) (4)**

Test Method	Test Method Number	Initial	Week 4*	Week 8*	Week 12*	(b) (4)
(b)			(4)			

(b) (4)

### 3.2.P.8.3 Stability Data

#### *Reviewed by SM*

The Applicant submitted stability data for the (b) (4) NT-501 PPQ/registration lots discussed above in section 3.2.P.8.1. All lots used in these studies were manufactured at Neurotech's facility (Cumberland, RI) and were stored under controlled environmental chambers at 37°C (b) (4). In these studies, (b) (4) was stored (b) (4), and (b) (4) lots were stored (b) (4) during the real time stability studies. This test protocol was implemented to assess the risks related to worst-case packaging interactions essential for a detailed stability assessment, while (b) (4) lots addressed performance under conventional storage conditions. This test methodology allows the demonstration of comparability between the (b) (4) storage configurations of NT-501.

The stability study data was reviewed and found acceptable. However, since the Applicant did not submit a detailed study protocol, it is difficult to know how many test articles were tested at each time point in the study and the number of replicates for each test article that were evaluated for each quality attribute. An information request was sent for a detailed study protocol. In response to the information request, the Applicant provided details of the stability protocol in three documents: 1. Provided an overview of the stability study, including details on the product, study phase, storage conditions, testing labs, the total units required for testing, study purpose, applicable specification, and the regulatory and manufacturing information; 2. Provided information on the tests performed at each stability timepoint throughout the study including details on how many NT-501 devices are required for each attribute tested at each time point and the number of samples tested for each test; 3. Provided information on the schedule for pulling samples at different time points for testing to monitor the product's stability over the study period of (b) (4) weeks. This information was reviewed and found to be adequate.

**Reviewer's comment (CP):** *An information request was sent October 31, 2024, asking the Applicant to clarify whether the monitoring device and the pH coloring guide proposed for packaging during commercialization were used in all shipping studies provided. This information was necessary to ensure that the temperature monitoring*

device and the pH color guide used in the DP packing for commercialization were adequately tested. The response was received in Amendment 62, dated November 8, 2024, and Neurotech confirmed that both the monitoring device and the pH color guide proposed for commercialization were used in all shipping studies provided in the submission. The response is acceptable.

**Overall Reviewer's Assessment (SM):** The stability study reports and response to two information requests were reviewed. The response to the two information requests are discussed above in section 3.2.P.8.1 and 3.2.P.8.3. The results from the (b) (4) PPQ lot stability studies support the proposed shelf life of NT-501 of 12 weeks when stored at 37°C protected from light. The stability studies use the same quality attributes that are used for product release. In addition to these parameters, container closure integrity (CCI) and product integrity, are assessed for stability evaluation. The studies also demonstrated that the product when stored inverted over the proposed shelf life is stable and is comparable to the product stored upright. The proposed shelf life is acceptable.

### 3.2.A APPENDICES

#### 3.2.A.1 Facilities and Equipment

*Reviewed by CP*

ENCELTO is manufactured at Neurotech Pharmaceuticals, Inc., located in Cumberland, Rhode Island (RI), US. The Cumberland, RI facility is approximately (b) (4), of which approximately (b) (4) is a dedicated modular cleanroom (constructed in 2009) located in the innermost portion of the building and designed to support the GMP manufacturing. The modular cleanroom designed and constructed in accordance with the Code of Federal Regulations (CFR) Title 21 Part 211 for Equipment, Buildings, and Facilities. The table below in this section includes the manufacturing areas, the classification of the rooms and the operations performed in each room.

**Table 65. Manufacturing area and associated operations.**

(b) (4)
---------

(b) (4)

The Applicant also provided the diagrams related to the room classification with the (b) (4) airflow, personnel flow, material flow, drug product flow, waste flow, mechanical HVAC colored plan, and equipment layout (Figures 29-35 below).





(b) (4)

AS BUILT DRAWING  
DO NOT USE FOR  
CONSTRUCTION

**Figure 29. Equipment Layout**

Table 58 provided below included the equipment used in the manufacturing facility.

**Table 66. Equipment Used in the Manufacturing of ENCELTO**

(b) (4)

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

(b) (4)

Table 67 below list the computer systems used in the facility.

**Table 67. Computer systems**

Computer Related System	System/ Equipment ID #	Qualification Document Number
(b)	(4)	

**Overall Reviewer's Assessment (CP):** *The Facilities and Equipment information provided in section 3.2.A.1 is sufficient to support the BLA. The flow controls for the manufacturing areas and equipment used are appropriate. Currently, ENCELTO is the only drug product manufactured at the Neurotech facility. Please refer to the DMPQ memo and the EIR memo for further information.*

### **3.2.A.2 Adventitious Agents Safety Evaluation**

Please refer to the review by KS below.

*Reviewed by KS*

According to 3.2.A.2.2.2, Neurotech has evaluated the potential for the introduction of adventitious agents into the manufacturing process by implementing a variety of risk mitigation processes and practices which includes the raw material quality system, the use of properly designed clean room manufacturing space, controlled movement of personnel and materials, and finally through the use of aseptic technique by the manufacturing personnel during open manipulation processing according to standard operating procedures and training accordingly. Below are the various potential sources of contamination:

- (b) (4)

Neurotech provided Table 1 in 3.2.A.2.2.2 showing the overall likelihood that an adventitious agent could contaminate NT-501. Based on their risk assessment, Neurotech concluded that there is a low to negligible risk of viral and non-viral adventitious agent contamination, including that from (b) (4) .

#### Adventitious agent safety evaluation for non-viral adventitious agents

Neurotech has evaluated the potential for the introduction of non-viral adventitious agents into the NT-501 manufacturing process by implementing a variety of risk mitigation processes and practices which include 1) the raw material quality system, 2) the use of properly designed clean room manufacturing space, 3) controlled movement

of personnel and materials, and 4) finally through the use of aseptic technique by the manufacturing personnel per SOPs and training.

Initial validation of the manufacturing process under study P0223 consisted of (b) (4) consecutive lots being manufactured and (b) (4) of each lot was tested per (b) (4). The sterility testing of NT-501 and corresponding primary package hold media met all acceptance criteria accordingly.

NT-501 lot release testing includes specifications for sterility, mycoplasma, and endotoxin, accordingly, to assure aseptic processing.

#### Adventitious agent safety evaluation for viral adventitious agents

Neurotech adventitious viral testing has been completed on the NTC-201-6A (b) (4). The test reports are provided in Section 3.2.S.2.3. In addition, the (b) (4) viral testing procedures and results are provided in Section 3.2.S.2.3.

(b) (4) tested has been shown to be free of adventitious agents.

Due to the continuous manufacturing process from DS to DP, Neurotech does not perform viral testing on (b) (4).

Neurotech utilizes (b) (4) manufacturing process and Endothelial-SFM (Endo-SFM; DMF(b) (4)) as the (b) (4) NT-501 DP hold media.

Neurotech has tested the (b) (4). A (b) (4) analysis of the cellular component of the (b) (4) was conducted. No exogenous transcripts were detected in the sample based on this analysis against (b) (4) entries within (b) (4) curated viral database.

**Reviewer's comment (KS):** The applicant provided a comprehensive assessment of adventitious agent safety for the (b) (4). Please refer to the reviewer comment (in Control of Starting (i.e., Source) Material(s) in Section 3.2.S.2.3 of this review memo) regarding adventitious testing conducted on the (b) (4). The (b) (4) analysis of the (b) (4), performed by (b) (4) was reviewed by Sandip De and Cinque Soto. While there were concerns about the sensitivity and specificity of the (b) (4) assays due to limited information on the (b) (4) and bioinformatics methods, the applicant clarified that the (b) (4) assay will not be used as a standalone test for detecting adventitious agents in manufacturing (b) (4), but rather as part of product characterization. In addition, the applicant clarified that the (b) (4) data is not a substitute for other conventional adventitious agent testing; it

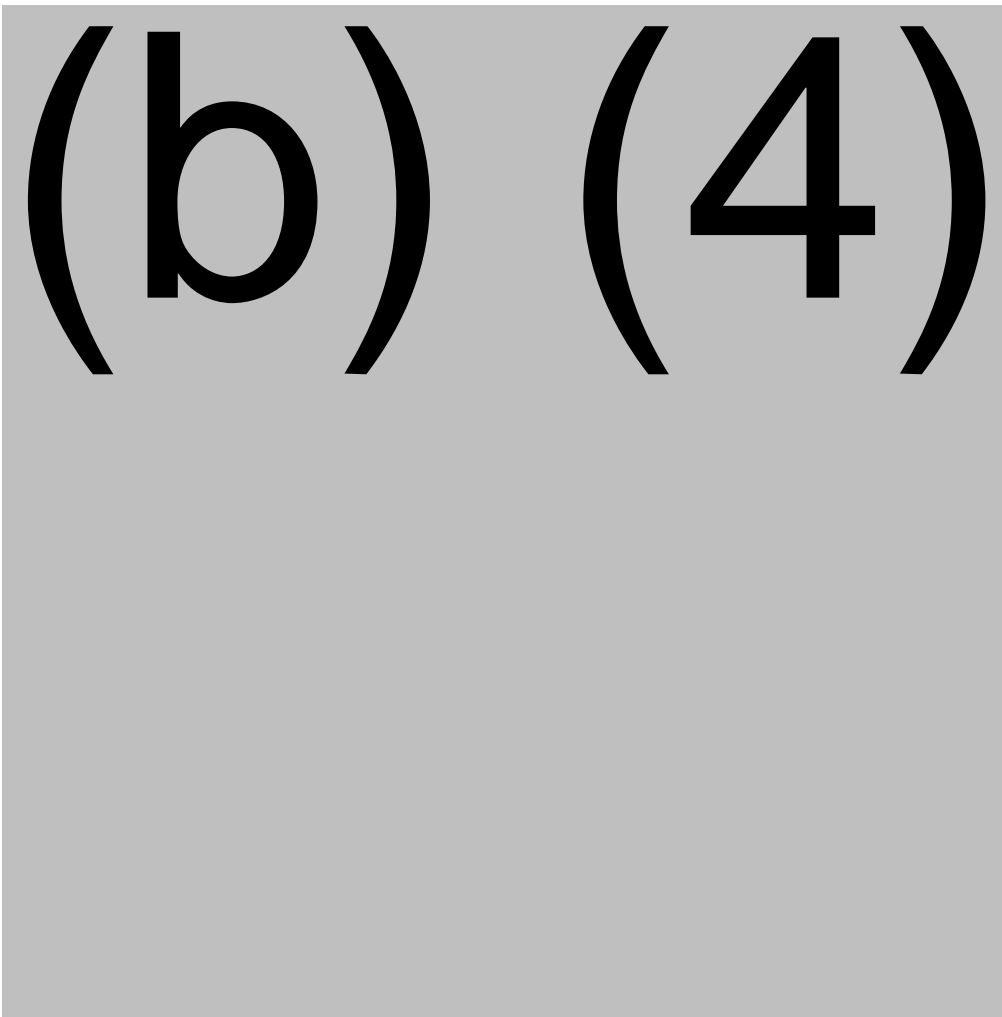
*was provided solely for informational purposes. The review team did not have any further major concerns, and the method is deemed acceptable for use in the characterization study. Please refer to the review memo provided by the Bioinformatics reviewers. Collectively, it was determined that the applicant's approach adequately mitigates risks associated with adventitious agents.*

Viral validation

Viral (b) (4) procedures are not conducted during manufacturing operations.

Viral validation is conducted on the raw materials of biological origin. This, in combination with the comprehensive viral testing on the raw materials (b) (4), provides assurance that the final NT-501 is free of viral contamination.

**Table 68. Vendor Viral Support on Raw Materials of Animal Origin**

A large rectangular area of the document is completely redacted, covered by a solid grey block. Overlaid on this grey block in large, bold, black font are the characters "(b) (4)", indicating that the content has been withheld under FOIA exemption (b)(4).

(b) (4)
---------

(b) (4)

(b) (4)

**Reviewer's comment (KS):** The original submission did not include the test report validating the effectiveness of (b) (4) for (b) (4) in the (b) (4) animal-derived components and (b) (4) (IR sent on October 4). In response to the IR (received on October 11, Amendment 47), the applicant provided information from (b) (4) regarding (b) (4) animal-derived components (b) (4) and one human-derived component (b) (4). It was stated that details on viral (b) (4) are included in Section 3.2.A.2 of MF (b) (4). The CMC reviewer of the MF confirmed that it is in good standing, with no remaining issues regarding these components.

- (b) (4)

(b) (4)

(b) (4)

In the study, a (b) (4)

**Reviewer's comment (KS):** The original submission did not include the test report validating the effectiveness of (b) (4) for (b) (4) (IR sent on October 4). In addition, the applicant did not provide test reports demonstrating the effectiveness of (b) (4) and (b) (4) (IR sent on October 4 and 31).

In response to the IR comment (received on October 11, Amendment 47), the applicant provided a test report demonstrating (b) (4). The data indicate significant viral (b) (4) exposed to (b) (4) below the minimum acceptable dose of (b) (4). While this information regarding (b) (4) is adequate, data on (b) (4) was not provided.






In response to a subsequent IR (received on November 8, Amendment 62), the applicant provided a test report from (b) (4) addressing (b) (4). The report states that no direct (b) (4) data for (b) (4) is available from the supplier. However, during manufacturing, the following steps are implemented to mitigate viral risks:

- (b) (4)

Additionally, literature on (b) (4) suggests that (b) (4)



(b) (4)



**Overall Reviewer's Assessment of Adventitious Agents Safety Evaluation (KS):**  
*Overall, the information provided regarding the Adventitious Agents Safety Evaluation is acceptable, with several deficiencies resolved during through IR communications, as summarized in the review memo above. No deficiencies remain outstanding.*

- ❑ **Viral Clearance Studies**  
Not Applicable (N/A).

### **3.2.A.3 Novel Excipients**

Not Applicable (N/A)

### **3.2.R Regional Information (USA)**

- ❑ **Executed Batch Records**

*Reviewed by CP*

The Applicant provided executes batch records from (b) (4) validation lot and master batch production records. Please refer to the tables below.

**Table 69. Executed Batch Records**

Batch No. <sup>a</sup>	Purpose
(b)	(4)

**Table 70. Master Batch Production Records**

Batch No.	Document
(b)	(4)

❑ **Method Validation Package**

*Reviewed by CP*

The method validations are reviewed and discussed in sections 3.2.S.4.2.and 3.2.S.4.3 Analytical Procedures and Validation of Analytical Procedures for Drug Substance and 3.2.P.5.2 and 3.2.P.5.3 for Drug Product.

**Reviewer's comment (CP):** *The information related to the executed and master batches records is sufficient as submitted in the BLA.*

❑ **Combination Products**

*Reviewed by KS*

This section provides device constituent description, verification/validation, quality, manufacturing, and control information for the DP device constituent, which are designed to encapsulate and protect the (b) (4) to allow continuous release of the cell produced ciliary neurotrophic factor (CNTF) and for insertion into the eye. Please refer to section 3.2.R.3 below for details on the device constituent of ENCELTO.

### **3.2.R.3 Device**

*Reviewed by KS*

#### Device manufacturers

- Neurotech Pharmaceuticals, Cumberland, RI (FEI: 3012545799; DUNS: 117685116)
  - Design control activities and testing of the NT-501 device constituents
  - Activities performed on site: design control activities, processing and contract testing for selecting raw materials, storage and release testing of sterilized pre-assembled capsule (PAC)

• (b) (4)

[REDACTED]

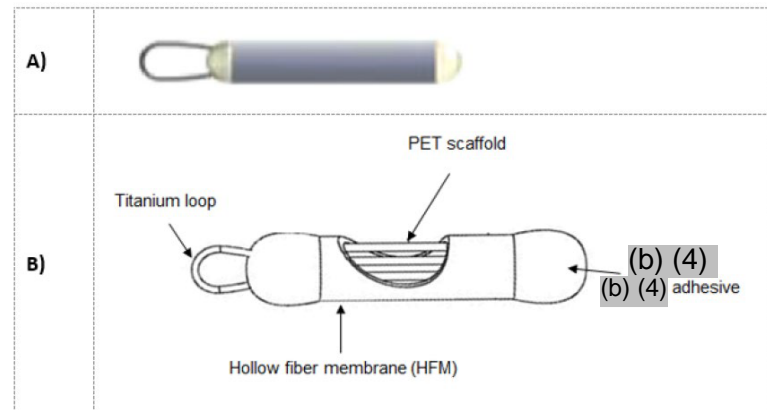
Neurotech states that activities at these sites in relation to the manufacture of the NT-501 device constituents are performed in accordance with 21 CFR part 820.

#### Device description overview

##### 1. NT-501 semi-permeable capsule

The primary NT-501 device constituent is the semi-permeable capsule (i.e., capsule) that is designed to house and protect encapsulated allogeneic retinal epithelial cells. The capsule is composed of a semipermeable (b) (4) hollow fiber membrane (HFM) containing an internal scaffold of (b) (4) of polyethylene terephthalate scaffold yarn, titanium fixation loop, sealed with a (b) (4) methacrylate (b) (4) adhesive (b) (4) (Figure 36).

The overall dimension of the capsule is (b) (4) mm long, with a external diameter of 1.2 mm. A titanium fixation loop attached to one end of the capsule is used to facilitate placement during insertion and retrieval upon removal.

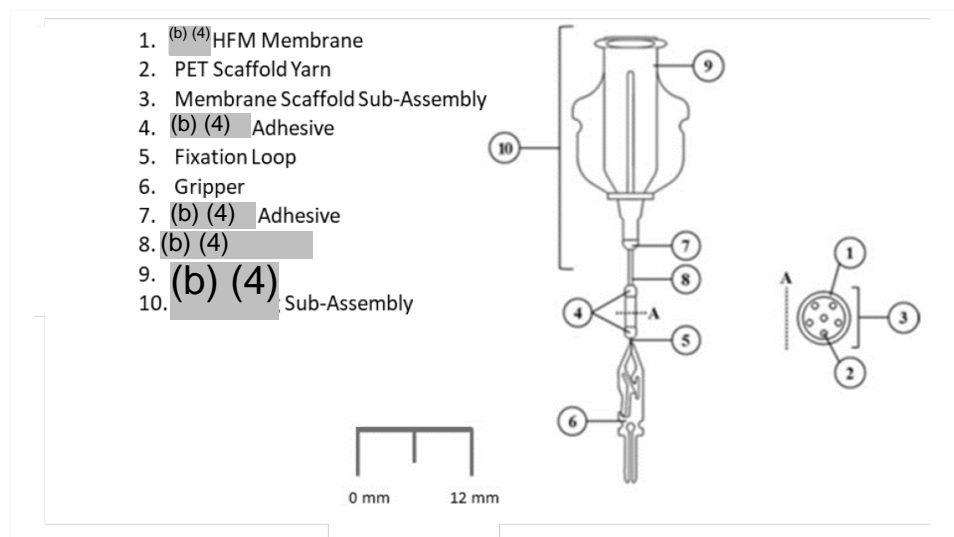


**Figure 30. NT-501 capsule (A) and cutaway representation of the capsule (B)**

## 2. NT-501 pre-assembled capsule (PAC)

Prior to encapsulation (cell injection), the empty NT-501 device constituent is known more specifically as pre-assembled capsules or PACs. As schematically detailed in Figure 37, each fully assembled PAC includes a (b) (4) and a titanium gripper.

This (b) (4) sub-assembly (#10 in Figure 37) is the main conduit for interfacing the semi-permeable capsule portion of the PAC with the encapsulation (b) (4) equipment.



**Figure 31. NT-501 PAC assembly**

Detailed device design description

1. (b) (4) hollow fiber membrane (HFM)

(b) (4)

The characterization data are used to establish the specifications shown in table 72 below for the HFM release by Neurotech to (b) (4).

**Table 71. Hollow Fiber Membrane Procured and Released by Neurotech to (b) (4)**

(b) (4)

## 2. PET scaffold (Yarn)

The scaffolding material consists of (b) (4)

procured and released by Neurotech manufacturing for further processing.

**Table 73. PET Scaffold Released for Further Processing**

(b) (4)
---------

## 3. (b) (4) medical adhesive

(b) (4)

**Reviewer's comment (KS):** The test report R257, titled 'Evaluation of (b) (4)

. An IR was sent on August 26, 2024 requesting either a test report using the NT-501 PAC configuration or a justification for applying the (b) (4) PAC data to NT-501 PAC.

In their response (received on September 4, Amendment 32), they explained that the adhesive (b) (4) is approximately (b) (4)

used to seal each end of the NT-501 PAC. Since the (b) (4) required for (b) (4)

#### 4. Fixation loop

The fixation loop (Figure 38) is fabricated from (b) (4) titanium alloy and meet (b) (4) class (b) (4) material classification. The anchor loop is secured by a gripper, which in turn is used for device handling and attachment of the NT-501 to its primary packaging container.



**Figure 32. Image of NT-501 fixation loop**

#### 5. NT-501 Gripper component

NT-501 gripper (or clip) attaches to the fixation loop of NT-501 and is used to facilitate packaging, handling, and implantation of the product. Following fixation loop insertion and adhesive seal, the gripper retention jaws are attached onto the fixation loop at a specified distance from the adhesive seal. Following cell encapsulation, the gripper is securely seated into a luer cap, which in turn is threaded into the NT-501 primary packaging.

At the time of implant, the luer lock cap/gripper unit provides a means of sterile presentation of NT-501 to the surgical field and the gripper is used by a surgeon to facilitate handling and implantation of the product. Once NT-501 is seated within the incision, the lever arm is depressed to release the gripper from the anchor loop.

Each gripper is (b) (4)

grooved grip point/insertion stop and luer cap insertion arms on the distal end for mating with NT-501 Primary packaging.

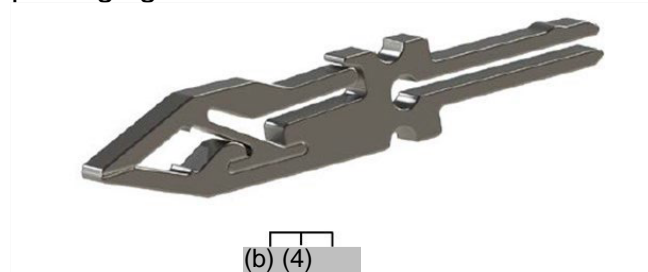


Figure 33. Image of NT-501 gripper


**Reviewer's comment (KS):** The gripper is used to facilitate packaging, handling, and insertion of the product. Each gripper is composed of 2 interlocking parts that form a jaw clamp. During the transport and storage, this gripper securely positions the drug product in liquid medium to sustain cells, and at the time of implant, the gripper assists the surgical implantation process. Once the product is seated within the incision, the lever arm is depressed to release the gripper from the anchor loop, so this is also serving as a surgical tool. Per our internal discussion, we decided to consider the gripper as both a primary packaging component of the container closure (since it is both in contact with the dosage form and will be serving to protect the dosage form) and a manual ophthalmic surgical instrument (Class I, 510(k) exempt manual ophthalmic surgical instrument) to deliver the dosage form. The gripper information has been reviewed by the CDRH consult reviewer (Alexander Beylin; ICC2400704). For a detailed evaluation, please refer to their consult review memo.

(b) (4), a contract manufacturer, carried out device stability testing on the NT-501 PAC. Each fully assembled PAC includes an empty NT-501 capsules, a (b) (4), adhesive, and an implant gripper. The PAC was subjected to (b) (4) accelerated (b) (4) using the (b) (4) protocol and the devices were tested for (b) (4) method. However, all of the tests performed were limited to the (b) (4) and provided no information about the stability of the gripper, which is a component of the PAC. We contacted the CDRH consult reviewer by email on September 24, 2024 to determine whether an IR should be sent to obtain additional information on gripper stability. In their response, the CDRH reviewer explained that they had consulted with Dr. Joe Hutter, a CDRH chemical SME, regarding the need for such information. Dr. Hutter stated that titanium is an extremely stable material and is unlikely to degrade or corrode in the storage liquid medium over the shelf life. He does not believe a gripper stability study is necessary and recommended leveraging titanium performance literature and inspecting the part after storage instead. I agree with their assessment, and no additional information is required for gripper stability. The grippers undergo visual inspection prior to use after storage.

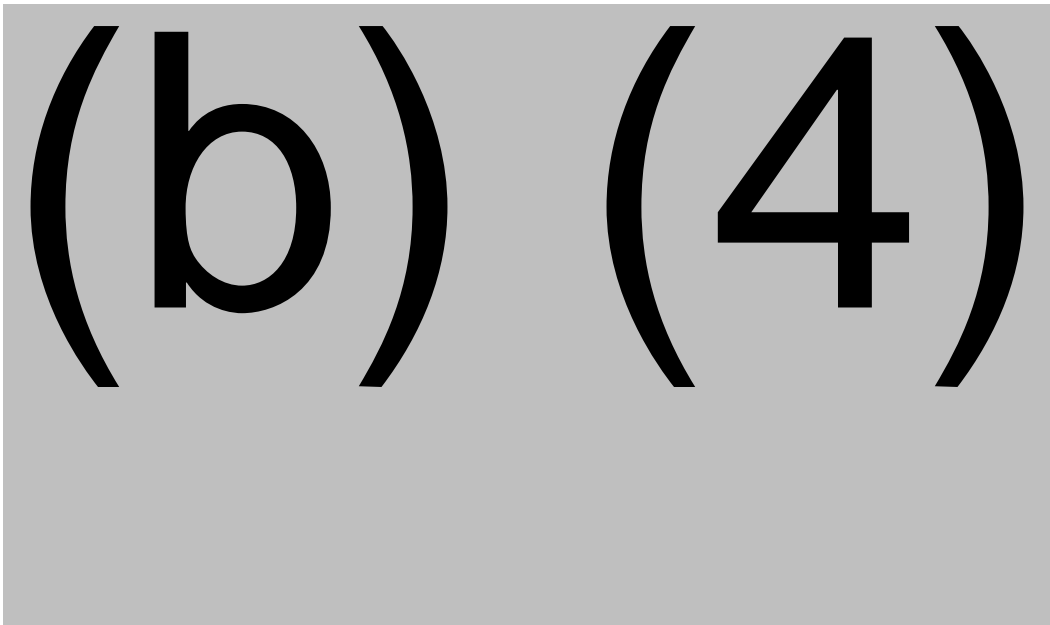
6. (b) (4)




(b) (4)

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(b) (4)

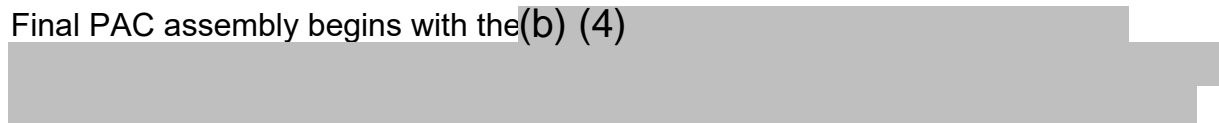
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(b) (4)

A large rectangular area of the document is redacted with a solid gray fill.

## 7. PAC Final Assembly

Final PAC assembly begins with the (b) (4)

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

### NT-501 PAC Device design history

The concept of encapsulated cell technology (ECT) and associated device design has evolved over 20 years of development efforts in both university and industrial laboratories. The earliest steps in device design began in the late 1980s within Brown University labs and was further developed and refined into a manufactured product during the 1990s at a Rhode Island biotechnology company called Cytotherapeutics for use in diabetes and CNS disease applications. Neurotech Pharmaceuticals transformed early development concepts, building on successful design iterations to arrive at a final concept for use as an intraocular implant. The applicant provides an overview of the historical development of the NT-501 device constituent including details on the studied device/cell configurations, IND reference, and clinical study identifiers. The table (Table 75) below shows the to-be-commercialized version. The NT-501-6A device utilizing (b) (4) and PET (b) (4) is the device version used in both Phase 3 investigations (NTMT-03A; NTNMT-03B).

**Table 74 75. The device/cell configuration of the to-be-commercialized version**

(b) (4)
---------

### Quality system

Neurotech has implemented a drug CGMP-based streamlined operating system in accordance with 21 CFR 4.4(b)(1) wherein the following provisions from the medical device Quality System Regulation (21 CFR 820) have been applied:

- 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

21 CFR 820.170 (Installation) and 21 CFR 820.200 (Servicing) are not applicable to NT-501. The following sections provide summaries of the procedures implemented at Neurotech to comply with each applicable quality system regulation provision.

**Reviewer's comment (KS):** *This device component does not require installation and servicing; therefore, I concur that 21 CFR 820.170 Installation and 21 CFR 820.200 Servicing do not apply to NT-501.*

## 1. Management responsibility


Neurotech states that Quality Management Responsibilities are outlined in SOP-1040. The procedure describes the Management Review process for the Quality Management System (QMS) at Neurotech Pharmaceuticals, Inc., and applies to management with executive responsibility at Neurotech in fulfilling the Management Responsibility requirements of 21 CFR 820. Management with executive responsibility (Executive Management) includes the CEO and those senior employees who have the authority to establish or make changes to the Quality Policy and Quality System. The Management Review Team performs quarterly reviews to evaluate the continuing suitability and effectiveness of the QMS in satisfying the requirements of U.S.QSR (21CFR 820), the Quality Policy and Quality Objectives.

***Reviewer's comment (KS):*** Please refer to the EIR for details on DMPQ's 483 items related to management responsibilities.

## 2. Design controls

Neurotech states that the design control process, SOP-8011 New Product Development, is divided into 5 phases: *concept, planning, development, evaluation, and commercialization*. A schematic overview of Neurotech's Design Control process is provided in Figure 43 below.

(b) (4)

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(b) (4)

(b) (4)

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Table 77 details a subset of design inputs designated as Essential Performance Requirements (EPR) which are evaluated after shipping, stability, and product lot

release. The EPRs were chosen because they are necessary for the NT-501 device constituent to encapsulate and protect the NTC-201-6A cells to allow continuous release of the cell-produced ciliary neurotrophic factor (CNTF). Some of the EPRs are designated as Critical Quality Attributes (CQA) of the combination product.

**Table 76. Essential Performance Requirements (a subset of design inputs)**

EPR	Related Design Input / Requirement	Target Requirement	Justification
PAC Integrity/ (b) (4)	(b) (4)	(b) (4)	Ensures adequate seal and membrane integrity of the NT-501 PAC
(b) (4)		(b) (4)	In conjunction with Identity testing, ensures NT-501 is secreting hCNTF and NTC-201-6A cells are performing as intended within NT-501.
Cell Viability		(b) (4) Viability; (b) (4)	Cell viability must be confirmed to ensure consistent NT-501 dosing performance.
Cell Number (b) (4)		200,000-440,00 cells/ NT-501	Cell number must be confirmed to ensure NT-501 dose is achieved.
NT-501 Sterility		Meets (b) (4) requirement	NT-501 must be confirmed sterile.

(b) (4)





Device design controls traceability matrix is developed. It is stated that the matrix demonstrates that, following Neurotech's design control procedure, the design outputs are adequately verified to meet the design inputs and the finished device is validated to meet the user needs (Table 78).

**Table 77. NT-501 Device Design Inputs and Verification**

Design Input Ref.	Design Input Description	Design Input Specification	Verification
(b) (4)			



(b) (4)



*Overall, the firm has implemented an effective process that balances purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.*

#### 10. Corrective and Preventive Action (CAPA)

SOP-1028 describes the Corrective and Preventive Action (CAPA) process which assures the tracking and trending of corrective and preventive actions requiring mid-term and long-term implementation plans at Neurotech. The CAPA System is used to track and trend corrective and preventative actions planned to address known issues or to implement preventive measures to mitigate the chance for a potential deviation.

These requirements apply to all cGMP operations and areas. This may include, but is not limited to:

1. Deviations/Non-conformance – Procedure
2. Product Complaints – Procedure for Handling Products
3. Complaints
4. External and internal audit observations
5. Annual Product Review (as appropriate)
6. Regulatory Concerns
7. Any issues that require mid-term and long-term corrective or preventative action



## 8. Recommendations following executed validation studies


Neurotech personnel of any department owning a deviation, out of specification, audit observations, inspection observations, complaints, event investigations, annual product review recommendations, or other issues which requires a mid-term or a long-term plan to implement corrective or preventative actions are responsible to initiate a CAPA in collaboration with Quality Assurance Department.

The CAPA documentation will include a clear description and timeline of all planned actions, completion dates, expected outcomes, required resources, renovations, and validations. After a minimum of (b) (4) days from the implementation of the CAPA, Quality Assurance will perform a verification of the effectiveness of the CAPA.

***Reviewer's comment (KS):*** During the PLI, several CAPA and deviation documents were reviewed. It was confirmed that the firm's CAPA process is effective in tracking corrective and preventive actions to address identified issues and mitigate the risk of potential deviations.

### NT-501 PAC device manufacturing

(b) (4)



A process flow diagram of the PAC manufacturing process is provided Figure 44.

(b) (4)

Raw material descriptions and incoming inspection

Neurotech's Quality Unit is responsible for ensuring that incoming raw material inspection and testing are completed and documented prior to Quality release of materials to (b) (4) or Neurotech for use in PAC manufacturing or PAC component preparation activities.

Upon receipt at Neurotech, all raw materials are identified with a unique raw material number. Each material is reviewed to establish that all certificates of conformance or any specified documentation are received, and samples are taken per applicable material specification by Quality personnel for appropriate testing.

(b) (4)

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

(b) (4)

#### 1. NT-501 Device constituent critical material stability program

The firm has established the stability period, stability testing, and storage conditions for the NT-501 device critical material components ((b) (4)

respectively. Their data show no aberrant values or degradation from initial testing of the materials. The (b) (4) adhesive has vendor expiry dating of (b) (4) .

#### 2. Establishment of NT-501 stability and expiry period of (b) (4) from date of manufacture

The NT-501 PAC expiry was established in studies:

- (b) (4)

In summary, Neurotech determined that the manufacture and packaging of the NT-501 sterile product provide appropriate level of protective support to the integrity and performance of the sterile PAC over a (b) (4) shelf-life period.

**Reviewer's comment (KS):** The PAC expiry period of (b) (4)

(b) (4)

An IR comment was sent on October 31, 2024, requesting additional information regarding the following:

○ (b) (4)

In response to this IR (received on November 8, 2024; amendment 62), the firm stated the following:

○ (b) (4)

The response is acceptable, given that the ongoing real-time (b) (4) study will eventually support the accelerated (b) (4) data. Additionally, the firm has established a robust strategy to manage and verify the expiry of PAC and other raw materials used in DP manufacturing.

**Overall Reviewer's Assessment of Combination Products Section (KS):** Overall, the information provided regarding the device constituent is acceptable, with several deficiencies resolved during the PLI and through IR communications, as summarized in the review memo above. No deficiencies remain outstanding.

❑ **Comparability Protocols**

Not Applicable (N/A)

**Other eCTD Modules**

**Module 1**

**A. Environmental Assessment or Claim of Categorical Exclusion**

*Reviewed by CP*

In accordance with 21 CFR 25.15(d), Neurotech affirms that the requested action, approval of the BLA for NT-501, qualifies for a categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(c) because action on the BLA does not significantly alter the concentration or distribution of the product, its metabolites, or degradation products in the environment. In addition to Neurotech's knowledge, there are no extraordinary circumstances indicating that the proposed action would significantly affect the quality of the human environment (21 CFR 25.21).

**Reviewer's comment (CP):** *In the original BLA, the Applicant claimed categorical exclusion from the requirement to prepare an environmental assessment under 21 CFR 25.31(a) (i.e., action on the BLA does not increase the use of the active moiety). An information request (dated August 9, 2024) was sent asking the Applicant to revise the categorical exclusion from 21 CFR 25.31(a) to 21 CFR 25.31(c) (i.e., action on the BLA does not significantly alter the concentration or distribution of the product, its metabolites, or degradation products in the environment) because the latter is more appropriate for the BLA. The Applicant provided the revised claim in Amendment 26 (date August 19, 2024).*

**B. Reference Product Designation Request**

Not Applicable (N/A)

**C. Labeling Review**

**Full Prescribing Information (PI):**

Dosage Forms and Strengths (3)

ENCELTO is a single-use implant that contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing rhCNTF (NTC-201-6A cell line) for intravitreal surgical placement. ENCELTO is an opaque semi-permeable capsule that is white to off-white, capped on both ends, and has a titanium loop on one end. ENCELTO width is  $1.2 \pm 0.1$  mm, length is  $6.1 \pm 0.4$  mm, and its internal diameter is  $0.88 \pm 0.02$  mm.

### Description (11)

ENCELTO (revakinagene taroretsel-lwey) implant, is single-use, sterile, nonpyrogenic and retrievable.

ENCELTO is an allogeneic encapsulated cell-based gene therapy product that contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing rhCNTF (NTC-201-6A cell line) for surgical intravitreal placement.

ENCELTO consists of an opaque, semi-permeable white to off-white capsule surrounding a scaffold of polyethylene terephthalate (PET) yarn, loaded with rhCNTF secreting allogeneic retinal pigment epithelial cells (NTC-201-6A cell line). Each end of the semi-permeable capsule is sealed with medical grade methacrylate adhesive, and to one end a titanium fixation loop is attached. ENCELTO width is  $1.2 \pm 0.1$  mm, length is  $6.1 \pm 0.4$  mm, and its internal diameter is  $0.88 \pm 0.02$  mm.

ENCELTO is packaged in a protective inner container within an orange to pink liquid hold medium referred to as Endothelial Serum Free Media (Endo-SFM), which is maintained sterile by a sealed outer container. ENCELTO is provided attached, by the fixation loop, to a gripper that both suspends ENCELTO in the Endo-SFM and facilitates intraocular insertion.

### Clinical Pharmacology (12)

#### Mechanism of Action

ENCELTO secretes recombinant human ciliary neurotrophic factor (rhCNTF), which is one of several neurotrophic factors endogenously produced by neurons and supporting glial cells. Studies have demonstrated that exogenous CNTF initially targets Müller glia to trigger a cascade of signaling events that promote photoreceptor survival; however, the mechanism of action for ENCELTO is not completely understood.

#### Pharmacokinetics

Systemic exposure of rhCNTF was measured in 2 distribution studies in rabbits and in 2 toxicology studies in minipigs. Overall, there was no evidence of systemic exposure to rhCNTF after implantation of ENCELTO in rabbits for periods up to 9 months or in minipigs for periods of up to 6 months.

Following intraocular implantation of a single ENCELTO dose in rabbits at 12 weeks, the mean  $C_{\max}$  of rhCNTF in the vitreous and aqueous was 2.0 and 0.3 ng/mL, respectively, and below the level of quantitation (LLOQ) in the serum and contralateral, untreated eye. Similarly in human patients, rhCNTF levels were below the limit for LLOQ in the serum.

#### Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of ENCELTO or of other products.

In a six-month Study NTMT-02B in which patients received ENCELTO in a single eye, one out of 31 patients (3%) tested positive for serum antibodies against the ENCELTO secreted product protein rhCNTF and one patient (3%) tested positive to serum non-secreted intracellular protein DHFR.

Because of the low occurrence of anti-drug antibodies, the effect of serum anti-rhCNTF and anti-DHFR antibodies on the safety or efficacy of ENCELTO is unknown

#### How Supplied/Storage and Handling (16)

1. Using the handle, remove the corepack from the larger shipping box.
2. Store ENCELTO in the corepack at 16° to 37°C (61° to 99°F) until ready for use.
  - Do not freeze, refrigerate, (b) (4)




Inspect the disposable temperature recording device. If a check mark is displayed, the ENCELTO has remained within the acceptable temperature range and may be used. If a “X” is displayed, the ENCELTO was exposed to temperatures outside the acceptable range and must not be used. Contact Neurotech immediately at (833)-963-9275.

- Protect ENCELTO from light.
3. Handle inner container (Figure 20) using sterile technique.
  4. Do not use beyond the “use by” date identified on the corepack label.
  5. Do not use ENCELTO if the pH is not within the acceptable range. Contact Neurotech immediately at (833)-963-9275.
    - Follow local institutional protocols to dispose of all ENCELTO materials and packaging after the procedure.
    - Orange to pink liquid hold medium referred to as Endothelial Serum Free Media (Endo-SFM) within packaging inner container may contain visible particles. Particle general description fiber, solid, white, or metallic in appearance.



## Carton and Container Label:

Please see below the carton (corepack) label and the container label for ENCELTO.

<b>revakinagene taroretcel-lwey</b> <b>ENCELTO™</b> Implant, for intravitreal use		NDC: 82958-501-01 <b>Rx Only</b> See instructions for Use for Implant Insertion Procedure	Manufactured by Neurotech Pharmaceuticals, Inc. 900 Highland Corporate Drive Building 1 Cumberland, RI 02864 U.S. License No.
One single-dose implant containing 200,000-440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotrophic factor (rhCNTF)		Administration route Intravitreal. Inactive ingredients: Endothelial Serum Free Hold Media (Endo-SFM) Product contains no preservatives. Store this package (closed) until ready for use. Shipment and Storage temperature: 61°F to 99°F (16°C to 37°C) Do not freeze or refrigerate. Keep protected from light.	
<b>Do not open until day of use</b> <b>Use-By Date: 2025-03-11</b> Product must NOT be used after the use-by date.		Dosage and Administration: See full prescribing information.	
 GTIN SN LOT DOM	(b) (4)	NDC  82958-501-01	

**Figure 39. Carton (corepack) Label**

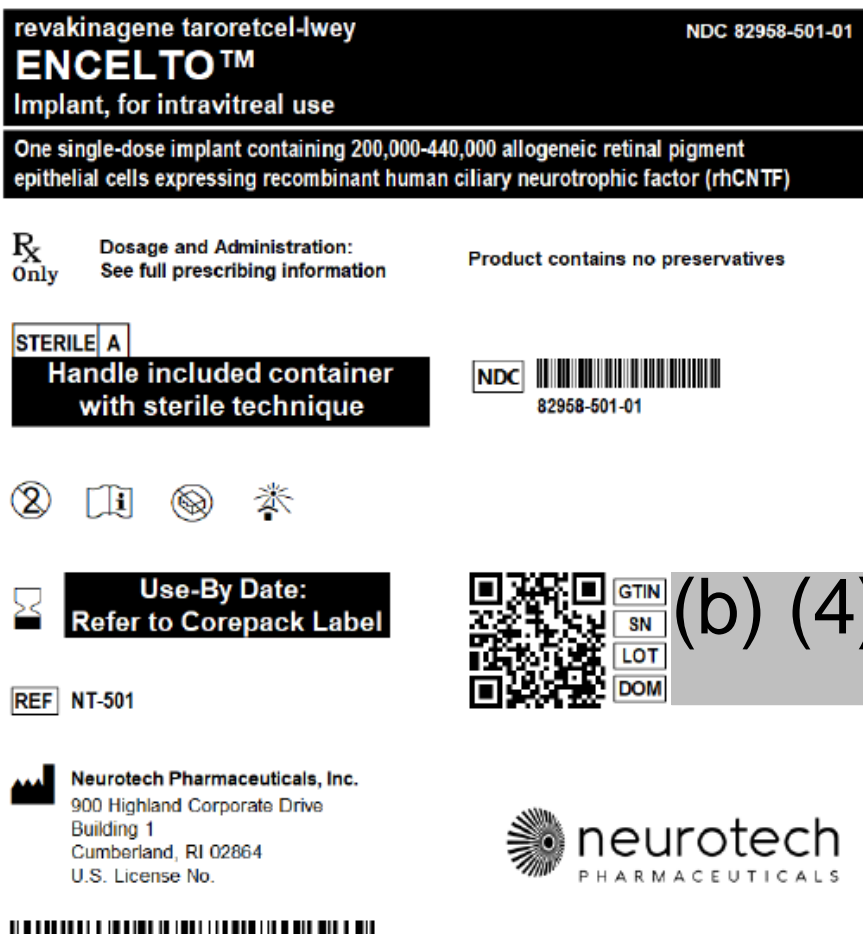


Figure 40. Outer Container Label

## Modules 4 and 5

### Module 4

#### Non-clinical Studies

The nonclinical development program evaluated a product representative of ENCELTO, NT-501. An early pharmacology study showed that the outer nuclear layer (ONL) in dogs with retinitis pigmentosa caused by rod-cone dysplasia type 1 (rcd1) was protected from photoreceptor loss following implantation of NT-501. A pharmacology study in healthy (b) (4) rabbits showed that secretion of 5 ng/day of rhCNTF following NT-501 implantation had no deleterious effects on photoreceptors, but that high doses of 22 ng/day of rhCNTF could have negative effects on cones. The nonclinical pharmacokinetic (PK) studies measured systemic exposure of rhCNTF in two distribution studies in rabbits and two toxicology studies in minipigs and pigs. There was no evidence of systemic exposure to rhCNTF after ITV implantation of NT-

501 in minipigs for up to 6 months or in rabbits for up to 9 months. In rabbits, NT-501 implants established CNTF levels averaging about 7-9 ng/day for up to 9 months. The effect of long-term ITV implantation of NT-501 was evaluated in a 3-part toxicology study in 4–8-month-old (b) (4) minipigs, 4–10-year-old (b) (4) pigs, and catastrophic device failure of NT-501 was evaluated by ITV injection of unencapsulated NTC-201-6A cells into 8-9 month old (b) (4) minipigs. Overall, data from this study suggests that the effects of NT-501 implantation were minimal: lens changes, focal refractive changes in the vitreous, and minimal to mild amounts of inflammatory cells and/or inflammation associated with the vitreous, the aqueous chamber, iris/ciliary body, and the corneoscleral junction. Although many of these appear to be triggered by the implantation of the NT-501 capsule itself or the implantation procedure, a dose-response to rhCNTF was present, with eyes implanted with empty capsules and capsules with a low CNTF output cell line exhibiting less intense changes than eyes implanted with NT-501. Microscopic analysis of ocular tissues corroborated these in-life findings. Intraocular pressures (IOP), pupillary response, cornea, and other clinical ophthalmic parameters were normal. ITV implantation of NT-501 did not cause any effects on systemic clinical signs, gross pathology, or histopathology of non-ocular organs.

Four Developmental and Reproductive Toxicity (DART) studies were conducted in rats and rabbits to establish the risks to fertility and teratogenicity associated with the subcutaneous (SC) administration of high doses of rhCNTF. In male rats administered rhCNTF at dose levels of 0, 10, 100, or 300 µg/kg/day subcutaneously (SC) for 62 days, there were no adverse effects on mating performance, fertility, or the postnatal development of the offspring. In female rats administered rhCNTF at dose levels of 0, 10, 100, or 300 µg/kg/day SC for 2 weeks prior to mating to postpartum Day 21, mating performance, fertility and gestational parameters were normal. No adverse effects on fetuses or pup postnatal development were reported. In pregnant rats administered rhCNTF at 10, 100, 300, or 1000 µg/kg/day SC on gestational Days 7-21, clinical changes were present in pregnant rats administered the highest dose level and decreased body weight gain was present at dose levels ≥100 µg/kg/day of rhCNTF. There were no rhCNTF-related teratologic changes reported in the fetuses. In pregnant rabbits administered SC rhCNTF at 2, 5, or 10 µg/kg/day SC on gestational Days 7-29, anorexia, abortion, and body weight loss occurred at 10 µg/kg/day. There were no rhCNTF-related teratologic changes reported in the fetuses.

A battery of genotoxicity studies was conducted to support licensure of NT-501 in keeping with ISO-10993, guidance for biological evaluation of medical devices. These studies included a (b) (4) study, (b) (4) study in mammalian cells, mouse bone marrow micronucleus study, and a Kligman maximization test. No genotoxicity was observed in these studies.

Studies to evaluate the carcinogenicity/tumorigenicity of ENCELTO were not conducted. These studies are not warranted based on the safety profile described in the provided toxicological risk assessments (TRAs).

**Reviewer's comment (CP):** The information summarized above was reviewed by Dr. Ernesto Moreira, pharm/tox reviewer for the BLA. Dr. Moreira indicated the nonclinical information provided supports approval of the BLA.

### Biocompatibility

The biocompatibility information related to the device constituent of ENCELTO is summarized in the table below. The reviewer's comments are also included in the table below.

**Table 78. Biocompatibility information and review**

<b>Biocompatibility Evaluation Endpoint:</b> (ISO 10993-1, CDRH 2016 Biocompatibility Guidance)		
<b>Biocompatibility Evaluation Endpoint:</b> (ISO 10993-1, CDRH 2016 Biocompatibility Guidance)	<b>Designation</b> <b>X</b> (For consideration) <b>O</b> (May be applicable) - Not applicable	<b>Subject Device:</b> (a) Based on internal discussion, the subject device is a NT-501 Semi permeable capsule – Configuration 2  (b) Contact profile: Direct tissue, as per internal conversation August 30, 2024.
<b><u>Permanent Implant with direct tissue contact</u></b>		<b>Biocompatibility reviewer comments and recommendations:</b>
Cytotoxicity: study (b) (4) Dated 2023	x	<b>Configuration-2 device.</b> The Applicant explained in response to IR dated September 20, 2024, use of the final packaged, sterilized, and sealed NT-501 (b) (4).  This comment applies to all biocompatibility reports submitted by the Applicant.  No negative results were reported in this cytotoxicity endpoint. The results are acceptable.
Intracutaneous/irritation reactivity/intraocular: (b) (4) Dated 2023	x	<b>Configuration-2 device.</b> No adverse reactions were identified in this Intracutaneous/irritation reactivity/intraocular endpoint. The results are acceptable.
Sensitization: (b) (4) Dated 2023	x	<b>Configuration-2 device.</b> No adverse reactions were identified in this Sensitization test. The results are acceptable.
Acute systemic: (b) (4) Dated 2023	x	<b>Configuration-2 device</b> was evaluated in (b) (4). Test (b) (4) was done on (b) (4). Both tests had passing results without any significant loss in animal weight or death reported. The results are acceptable.
(b) (4) Dated 2023	o	<b>Configuration-2 device.</b> No adverse reactions were identified in this (b) (4) test. The results are acceptable.
(b) (4) Toxicity: (b) (4) Dated 2002	x	<b>Configuration-1 device</b> (NT-501 PAC device) was evaluated in this study. I reviewed the (b) (4) report and the provided results are acceptable. However,

		as in the case of (b) (4), this endpoint is also leveraged from the long-term animal implantation study as per "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff". Information provided for this endpoint is acceptable.
Genotoxicity: (b) (4) Dated 2023	x	<b>Configuration-2 device.</b> No negative results were reported in either (b) (4) tests. The results are acceptable.
Hemolysis : study (b) (4) Dated 2023	x	<b>Configuration-2 device.</b> No adverse reactions were identified in this Hemolysis test. The results are acceptable.
Chronic toxicity: studies usually have a duration of (b) (4). Dated 2002.	o	<b>Configuration-1 device (NT-501 PAC device).</b> This endpoint is listed in the ISO 10993-1 guidance as optional and was not provided. However, information for this endpoint is leveraged from the long-term implantation study as per "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" Guidance for Industry and Food and Drug Administration Staff". Test results from the long term animal implantation study TI250-802, th035-800, 2 and 26 weeks long were acceptable as they have not showed any significant adverse events.
Implantation : TI250-802, th035-800, 2 and 26 weeks long, Dated 2002	X	<b>Configuration-1 device (NT-501 PAC device)</b> Although the implantation study was performed on (b) (4) (as in the final finished device) and featuring a PET Scaffold Yarn made of the same material but provided by a different supplier. The provided results are acceptable because: 1. (b) (4) constitute evaluating worst-case design . 2. Use of (b) (4) is typical in medical device industry as the (b) (4) without any adverse events or issues reported, as of 9/27/24. Please see the "Device-Background" listed above for more information. 4. All the new test reports, including (b) (4) performed on (b) (4)

		<p>with (b) (4) showed passing results without any major negative events reported. The report indicates no major long term adverse events. Only expected normal tissue reaction to foreign body was reported (macroscopic: not significant tissue contact irritation and microscopic: nonirritant comparable to negative control). All animals maintained or gained weight and survived 26 week long test. The provided results are acceptable.</p>
Carcinogenicity	o	<p>This is optional endpoint. A copy of the waiver was provided by Dr. Panico on 9/3/24. I reviewed the provided waver information and agree no carcinogenicity endpoint is needed to be evaluated. The Applicant discussed wealth of supporting evidence, such as:</p> <p>(a). Based on studies in animals and humans, CNTF levels delivered by NT-501-6A.02 achieve the desired pharmacological effects in the target organ (eyes).</p> <p>(b) The lack of evidence of off-target proliferative, hyperplastic, preneoplastic, or neoplastic effects for CNTF in epidemiological studies, toxicological studies, or human case reports pertaining to exposure to CNTF and subsequent carcinogenic effects.</p> <p>(c) Relevant toxicokinetic and toxicodynamic data from animal studies (Study R331; Study P0008) indicate that CNTF has a very short systemic half-life and does not bioaccumulate. Animal studies and human studies consistently demonstrate that continuous local release of CNTF from implanted NT-501 does not result in systemic exposure to CNTF proteins.</p> <p>(d) Low systemic and local toxicity concern associated with the residual human endothelial SFM contained in NT-501.</p> <p>(e) Lack of mutagenic and clastogenic potential of the (b) (4) based on in vitro and in vivo genotoxicity studies conducted on (b) (4)</p> <p>(f) Low carcinogenicity potential of the SFM based on a weight of evidence evaluation of existing genotoxicity and carcinogenicity data as well as modeling data. For more detailed justification, please refer to the explanation provided in the "REQUEST FOR WAIVER OF CARCINOGENICITY STUDIES"</p>
Toxicological Risk assessment of (b) (4) : device:NT-501 PAC. File: NT04-0118	-	<p>Not required as per ISO 10993-1. As discussed on 9/10/24 during our internal meeting, this report will be or was already reviewed by Dr. Sarafanov (Chemist/TRAs).</p>

NT-501 impurity and Stability assessment device:NT-501 PAC. File: P0220	-	Not required as per ISO 10993-1. As discussed on 9/10/24 during our internal meeting, this report will be or was already reviewed by Dr. Sarafanov (Chemist/TRA).
Immunotoxicity evaluation of NT-501 PAC (computational analysis) device:NT-501 PAC. File: NT06-0318	-	Not required as per ISO 10993-1. As discussed on 9/10/24 during our internal meeting, this report will be reviewed by Dr. Moreira (TRA-P/T)

**Reviewer's comment (CP):** A consult was requested (August 1, 2024) for the review of the biocompatibility of the device constituent of ENCELTO. The consult, Dr. Wojtek Tutak, CBER/OTP/OCTHT/DCT2/TEB2, provided his review (summarized above) October 10, 2024, and indicated the information was reviewed and found acceptable to support safe use of the device constituent in ENCELTO for the purpose of the BLA.

#### Module 5

BLA 125798 is supported by safety and efficacy data from six (6) clinical studies: (i) Phase 1 study (NTMT-01), (ii) Phase 2 study (NTMT-02), (iii) a noninterventional long-term safety and efficacy Study NTMT-01/02E (main study), which included an interventional Substudy NTMT-01/02E-SS, (iv) Study NTMT-02-B, which evaluated bilateral administration of NT-501 implants, and two Phase 3 studies, (v) NTMT-03-A and (vi) NTMT-03-B.

Substantial evidence of effectiveness is established based on two adequate and well-controlled Phase 3 studies, NTMT-03-A and NTMT-03-B, which were identical in design (including efficacy endpoints, total duration, and enrolled population).

The primary efficacy endpoint in both studies was the rate of change in the area of EZ loss (IS/OS; macular PR loss) from baseline through Month 24, as assessed using SD-OCT in the study eye of patients with MacTel. The EZ, as depicted in ocular coherence tomography, is the portion of the inner segment of the photoreceptors that is immediately adjacent to the junction between photoreceptor inner and outer segments, and its integrity and intensity are important indicators of PR health. Significant thinning and break in EZ are seen with PR degeneration and loss. Secondary efficacy endpoints by order of hierarchical testing were: (i) the mean change in aggregate sensitivity loss of microperimetry within the EZ line break area from baseline to Month 24, (ii) mean change in monocular reading speed from baseline at Month 24, and (iii) mean change in the National Eye Institute-Visual Function Questionnaire (NEI-VFQ-25) near activities subscale score from baseline at Month 24 (The near activities subscale score was an average of the scores for items 5, 6, and 7 in the NEI-VFQ-25.).

Both studies met their primary endpoint and demonstrated that NT-501 slowed the rate of disease progression over 24 months. The mean rate of change in EZ area loss from baseline over 24 months was 0.075 (0.012) mm<sup>2</sup> / 24 months in the NT-501 group and 0.166 (0.013) mm<sup>2</sup> / 24 months in the sham group, with a statistically significant difference between groups (-0.091 [0.018] mm<sup>2</sup>; 95% CI: -0.125, -0.056; p<0.0001) in Study NTMT-03-A. For study NTMT-03-B the mean rate of change was 0.111 (0.0142)

mm<sup>2</sup>/24 months in the NT-501 group and 0.160 (0.0149) mm<sup>2</sup> / 24 months in the sham group, with a statistically significant difference between groups (–0.0486 [0.0206] mm<sup>2</sup>; 95% CI: –0.089, –0.0082; p =0.0186). The exhibited differences in both studies exceeded the measurement uncertainty, of 0.0132 mm<sup>2</sup> (SD=0.0114 mm<sup>2</sup>) of intra-grader variability and 0.018 mm<sup>2</sup> (SD=0.0343 mm<sup>2</sup>) of intergrader variability including an arbitrator, making the change clinically meaningful. These differences correspond to a 54.8% reduction in the rate of retinal degeneration through 24 months in Study NTMT-03-A and a 30.6% reduction in Study NTMT-03-B.

Study NTMT-03-A also met its first secondary efficacy endpoint, demonstrating that NT-501 slowed the aggregate retinal sensitivity loss from baseline through Month 24. Although there was a mean increase in aggregate retinal sensitivity loss from baseline to Month 24 in the NT-501 and sham groups, the magnitude of loss was smaller in the NT-501 group compared to the sham group (25.3 versus 43 decibels (dB), respectively; p=0.02). For Study NTMT-03-B, the difference between NT-501 and sham in the change in aggregate retinal sensitivity loss from baseline to Month 24 was smaller in the NT-501 group relative to the sham group (40.02 versus 41.97 dB) but the difference was not statistically significant (p=0.83). For most of the remaining secondary endpoints, differences favored the NT-501 implant group.

Safety of NT-501 was evaluated in three different pools. NTMT-03-A and NTMT-03-B were used to evaluate safety in Pool 1 and were used to provide the safety information in the United States Prescribing Information (USPI).

Pool 2 included Studies NTMT-01, NTMT-02, NTMT-01/02E, NTMT-02-B in addition to the two Phase 3 studies described above. Pool 3 consisted of all patients who received NT-501 implant across all indications (which also include retinitis pigmentosa [RP], geographic atrophy [GA] associated with age-related macular degeneration [AMD], and achromatopsia).

There were no deaths and no cases of infectious endophthalmitis. The rate of explantation was low across all studies. Suture-related complications was the most common adverse reaction due to the procedure encountered with higher frequency in the treatment group. Delayed dark adaptation and miosis were the only AEs related to NT 501 or ciliary neurotrophic factor (CNTF) and were reported in 20.9% and 18.2% of patients across all MacTel studies.

Overall, the efficacy and safety data in this BLA support a favorable benefit-risk profile for patients with MacTel. NT 501 is effective in slowing down the progression of disease in patients with MacTel, NT 501 was well-tolerated for a period of up to 9 years after intraocular implantation.

**Reviewer's comment (CP):** *The clinical information summarized above was reviewed by the clinical reviewer of the BLA, Dr. Ekaterini Tsilou, CBER/OTP/OCE/DCEGM/GMB2. Dr. Tsilou indicated that, based on the favorable benefit-risk profile and the lack of available treatment options for MacTel type 2, the clinical review team recommends traditional approval of this BLA.*