

BIOINFORMATICS Consult Review Memorandum

BLA STN 125798

**Neurotech Pharmaceuticals, Inc.
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Reviewer/Title/Affiliation	Signature and Date
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Executive Summary

Neurotech has contracted (b) (4) to perform adventitious agent testing using (b) (4) (referred to as (b) (4) method uses (b) (4). Neurotech supplied (b) (4) samples to (b) (4) for testing ((b) (4)). All (b) (4) samples tested negative for adventitious agents. We initially had concerns about the sensitivity and specificity of (b) (4) assay due to lack of information on the (b) (4) and bioinformatics methods. Upon corresponding with the Applicant during the BLA review (see IRs below), the Applicant provided additional details and clarified that they will only use the (b) (4) assay as part of product characterization (see IR#2). The Applicant does not plan to use the (b) (4) assay as a stand-alone assay for the detection of adventitious agents in manufacturing, (b) (4) testing, (b) (4) testing, (b) (4). We have reviewed (b) (4) method and do not have major concerns. (b) (4) method is acceptable for use as part of the characterization study, (b) (4), submitted in Section 3.2.A.2.

SCOPE

This consult review is focused on assessing the (b) (4) adventitious agent testing (AAT) method for the proposed use in the BLA. The (b) (4) AAT method uses a (b) (4). The details of the (b) (4) preparation and bioinformatics methods are described in (b) (4) Master File (MF) (b) (4) which included multiple amendments submitted to MF (b) (4). Certain detailed information missing in MF (b) (4) was requested to the Applicant through IRs. All the files reviewed are found in **Table A1** in the appendix.

BACKGROUND

- (b) (4)

Conclusion

We have reviewed the (b) (4) methods used by Neurotech to characterize the (b) (4) from a previous (b) (4) lot for any adventitious agents. We had concerns about the (b) (4) method used by Neurotech as provided by their CRO, (b) (4). Most serious concerns were a lack of detail in the (b) (4) preparation, quality control (QC) metrics, and details of the bioinformatics methods used to detect a (b) (4). Upon corresponding with the Applicant during the BLA review (*see* IRs below), the Applicant provided additional details on their (b) (4) preparation and bioinformatics methods. Additionally, the sponsor clarified that they will only use the (b) (4) assay as part of product characterization (*see* IR#2) and do not plan to use the (b) (4) assay as a stand-alone assay for the detection of adventitious agents in manufacturing, (b) (4) testing, (b) (4) testing, (b) (4) testing. The (b) (4) methods used by Neurotech to characterize the (b) (4) are acceptable. .

Bioinformatics IRs #1 (September 5, 2024)

You use (b) (4) Adventitious Agent Testing method to detect adventitious viral agents in Applicant samples. The method uses (b) (4). The acceptability of your method will depend on several factors that include method performance (sensitivity, specificity, accuracy, precision, etc.) in detecting known and unknown adventitious agents, suitability of positive/negative controls, reference standards, and the completeness of the viral reference databases. Please address each comment below by **COB August 23, 2024**.

1. Please submit a comprehensive validation study report showing the performance of (b) (4) Adventitious Agent Testing method.

Neurotech's Response

The (b) (4) Assay Validation Summary Report provides a high-level summary of the validation parameters.

Full details of the validation can be found in (b) (4) MF (b) (4) as authorized in (b) (4) Letter of Authorization.

(b) (4) also provided their Technical Specification for Assay Performance, which outlines the related Standard Operating Procedure (SOP) and validation reports related to Neurotech (b) (4) test samples' (b) (4) study project number (b) (4) (Table 2).

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

Neurotech's Response

The (b) (4) acceptance criteria for the (b) (4) quality can be found in the following Neurotech (b) (4) study workbooks provided by (b) (4). Please refer to the analysis section within the (b) (4) on (b) (4) system. With respect to the quality metrics and alignment metrics, please refer to the (b) (4) MF (b) (4).

Reviewer Assessment

Bioinformatics could not locate quality control (QC) metrics in MF (b) (4). We will submit another IR requesting that the QC information be provided for our review. (Note. This issue was resolved in IR #2 and IR#3).

4. Please provide a sufficiently detailed description of the software tools used in your bioinformatics analysis to facilitate our assessment of the adequacy of your approach and to reproduce your bioinformatics workflow, if necessary. Please also provide a detailed description of the software tools you use in your bioinformatics analysis. Please provide:
 - a. a list of bioinformatics software that you will use with sufficiently detailed information such as the version of the tool, licensing information, publication information, OS/hardware system requirements, and software repository information
 - b. command line interface (CLI) information on how each bioinformatics software tool will be used in your workflow. The information should include command line information of the software tool with input/output parameters and a description of the contents of the output files used in downstream analyses

We have provided you with an Excel workbook with filename **Software_tools_and_CLI_v0.2.xlsx**. The Microsoft Excel workbook is being provided as a convenience to you and does contain an exhaustive list of important software fields. You should include any additional software fields that would allow us to evaluate your bioinformatics analysis procedures more effectively.

Neurotech's Response

Full details of bioinformatics software including the licensing information, publication information, OS/hardware system requirements, and software repository information can be found in (b) (4) MF (b) (4).

Reviewer Assessment

Bioinformatics could not locate this information in MF (b) (4). Bioinformatics will submit another IR requesting this information. (Note: This was resolved in IR#2).

5. Please describe how you handle cases where the (b) (4) under consideration is not present in the (b) (4) database.

Neurotech's Response

Please refer to the (b) (4) Assessment memo included with this response. Additional details can be found in (b) (4) MF (b) (4)

Reviewer Assessment

The response provided by the Applicant is acceptable.

6. Please provide a flowchart detailing the bioinformatics workflow.

Neurotech's Response

Full details of the bioinformatics workflow can be found in (b) (4) MF (b) (4).

Reviewer Assessment

A flowchart describing the overview of the (b) (4) appears in MF (b) (4). The flowchart provided by the Applicant lacked sufficient detail. Bioinformatics will submit another information request to the Applicant. (Note: This issue was resolved in IR #2).

Bioinformatics IRs #2 (October 4, 2024)

You tested adventitious agents in (b) (4) using in (b) (4) and other methods (per ICH (b) (4) and (b) (4)). In addition, you used (b) (4) to specifically detect potential viral contamination introduced during the NT-501 (b) (4) steps involved in creating the (b) (4). Please respond to the information requests below:

1. We recommend conducting matrix-specific validation of the (b) (4) assay if you plan on implementing (b) (4) as a stand-alone assay for the detection of adventitious agents in your (b) (4) in the future.

Neurotech's Response

Neurotech does not plan to introduce a (b) (4) assay as a stand-alone assay for the detection of adventitious agents in the manufacturing nor release of (b) (4) in the future. (b) (4) was executed on the (b) (4) solely as a part of the characterization study, (b) (4) submitted in Section 3.2.A.2.

Reviewer Assessment

The Applicant will not be using (b) (4) on their product release. Thus, product-specific validation on their (b) (4) method may not be required. The use of (b) (4) as a supplemental method is acceptable.

2. While your current (b) (4) assay validation includes (b) (4) viruses, this is insufficient for detecting (b) (4) DNA viruses. If you intend to use (b) (4) as a stand-alone

assay for adventitious agent detection in (b) (4), we recommend validating the assay for (b) (4) DNA viruses.

Neurotech's Response

Neurotech does not plan to introduce an (b) (4) assay as a stand-alone assay for the detection of adventitious agents in the manufacturing nor the release of (b) (4) in the future.

Reviewer Assessment

The Applicant will not be using (b) (4) as part of their manufacturing process nor in the release of (b) (4). Thus, product-specific validation on their (b) (4) method may not be required.

3. Please clarify whether you plan to use (b) (4) for adventitious agent testing (AAT) in the (b) (4), or if you intend to implement (b) (4) for AAT in (b) (4) manufactured in the future.

Neurotech's Response

Neurotech would like to clarify that we do not plan to use (b) (4) for AAT in the (b) (4) nor do we intend to implement (b) (4) for AAT in (b) (4) manufactured in the future.

Neurotech executed (b) (4) on the (b) (4) form as required for assay execution and the corresponding (b) (4) on a (b) (4) solely as a characterization study in support of the Section 3.2.A.2 risk assessment.

Reviewer Assessment

The Applicant will not be using (b) (4) detection as part of their manufacturing process nor in the release of (b) (4). Thus, product-specific validation on their (b) (4) method may not be required.

4. You provided a LOA for MF (b) (4) that contains information on (b) (4). You responded to our comments (dated **August 26, 2024**, see below) by stating that the information we requested can be found in MF (b) (4). Please provide the MF sequence number (SN) where we can find the information to address each comment below:
 - i. You provided Q30 acceptance criteria for your (b) (4) quality (see Adventitious Agent Testing (AAT) Results, Appendix I). Please provide additional

(b) (4) quality metrics and alignment metrics for your analysis. These metrics should accompany acceptance criteria where appropriate. We have provided you with an Excel workbook with filename (b) (4)_qc+metadata_v0.2.xlsx. This workbook contains generally accepted QC metrics and alignment statistics for assessing (b) (4) quality (see worksheets Library metadata and Run_(b) (4)_qc+metadata_v0.2.xlsx is being provided as a convenience to you and does not contain an exhaustive list of QC metrics and alignment statistics. You should include any additional information that will allow us to evaluate your bioinformatics analysis more effectively. Please note that acceptable file formats for associated metadata are CSV, JSON, or Microsoft Excel.

Neurotech's Response

Neurotech has previously executed (b) (4) as a characterization only of a (b) (4) to support a viral risk assessment (Section 3.2.A.2 of the original BLA).

Please note that Neurotech has repeatedly contacted (b) (4) to provide more detailed information on the raw data for Q30 acceptance criteria for the (b) (4) quality from the characterization study to support the original IR# 21 request. Neurotech has also reached out further this week regarding this IR# 32 question. Unfortunately, (b) (4) has requested additional time to gather the requested data. As such, Neurotech will provide as a follow up to this IR as and when (b) (4) provides the requested information.

Reviewer Assessment

Since the Applicant will not be using (b) (4) for drug product (DP) (b) (4) many of quality metrics (QC) BI uses to evaluate (b) (4) quality may not be necessary. This issue has been resolved in IR #3 – see **Table 3** as well.

ii. Please provide a sufficiently detailed description of the software tools used in your bioinformatics analysis to facilitate our assessment of the adequacy of your approach and to reproduce your bioinformatics workflow, if necessary. Please also provide a detailed description of the software tools you use in your bioinformatics analysis. Please provide:

- a) a list of bioinformatics software that you will use with sufficiently detailed information such as the version of the tool, licensing information, publication information, OS/hardware system requirements, and software repository information
- b) command line interface (CLI) information on how each bioinformatics software tool will be used in your workflow. The information should include command line information of the software tool with input/output parameters and a description of the contents of the output files used in downstream analyses

We have provided you with an Excel workbook with filename ***Software_tools_and_CLI_v0.2.xlsx***. The Microsoft Excel workbook is being provided as a convenience to you and does contain an exhaustive list of important software fields. You should include any additional software fields that would allow us to evaluate your bioinformatics analysis procedures more effectively.

Neurotech's Response

Neurotech reached out to the contract lab, (b) (4), regarding the Agency's request for information and the following information has been communicated to Neurotech:

- (b) (4) is located within (b) (4) BMF (b) (4). However, (b) (4) noted that the Agency-requested information regarding CLI "may also be in (b) (4) has communicated to Neurotech that this information will be submitted as (b) (4) to BMF (b) (4) by a target date of October 11, 2024, to fulfill the Agency's request for information on behalf of Neurotech.
- VPLAN000113, located within (b) (4) BMF (b) (4), contains overall architecture of the algorithm.

5. Please provide a flowchart detailing the bioinformatics workflow.

Neurotech's Response

Neurotech is awaiting a response from (b) (4) regarding this requested information. Neurotech will provide any information (b) (4) provides to address this request as soon as it is available.

Reviewer Assessment

The information provided by the Applicant is acceptable.

Bioinformatics IRs #3 (November 7, 2024)

QUESTION 4

In our information request, dated October 4, 2024, we requested additional information on (b) (4) quality, sequence alignment metrics, and a detailed flowchart depicting the bioinformatics workflow. You responded by stating that (b) (4) requested additional time to gather the requested data. However, a timeline was not provided. Please provide a timeline for when (b) (4) plans to submit this data to MF (b) (4). If (b) (4) has already submitted the data to MF (b) (4), please provide the related sequence number (SN).

Neurotech's Response

As previously communicated in response to IR #32 (Question 5) that was submitted on October 4, 2024, Neurotech has made multiple requests to (b) (4) to address the Agency's request

for additional information on the (b) (4) testing performed for Neurotech, and even more recently regarding any updates they can provide to outstanding responses to Question 5 of IR #32. Neurotech also provided to (b) (4) the FDA excel worksheets, (b) (4) raw data, and software-tools/CLI to complete and either return to Neurotech or update their BMF. The following are what has been provided from (b) (4) :

(b) (4) _qc+metadata_v0.2.xlsx

Neurotech has extracted the relevant applicable information from the (b) (4) study workbooks that were previously provided to the FDA (b) (4) and incorporated the information into the FDA-provided spreadsheet (b) (4) _qc+metadata_v0.2). Neurotech also had a teleconference with (b) (4) subject matter experts on November 7, 2024, wherein (b) (4) communicated that some of the cells in the FDA-provided spreadsheet were not applicable to the Neurotech (b) (4) study, and as such those cells are noted as N/A in the attached worksheet. However, (b) (4) also reviewed columns AB through AV that Neurotech added to the spreadsheet as they are applicable to assist with the FDA's review. Software_tools_and_CLI_v0.2.xlsx (b) (4) communicated that the BMF was updated to include this information and can be found in (b) (4). An updated Letter of Authorization (LoA) was provided to Neurotech and is included with this submission (see Appendix 2).

Software_tools_and_CLI_v0.2.xlsx

(b) (4) communicated that the BMF was updated to include this information and can be found in (b) (4). An updated Letter of Authorization (LoA) was provided to Neurotech and is included with this submission (see Appendix 2).

Flowchart for Bioinformatics Workflow

(b) (4) has confirmed that the requested flowchart detailing the bioinformatics workflow information was added to the BMF (b) (4) wherein (b) (4) to the BMF now include "analyticalanalytical-procedures-oprd2039" (eCTD Sequence: 0004) and "analyticalanalyticalprocedures-oprd2040" (eCTD Sequence: 0035), respectively, with the relevant updates. Please refer to updated LoA to Neurotech Pharmaceuticals, Inc. From (b) (4) (Appendix 2). Furthermore, for ease of FDA review, (b) (4) communicated that the following bioinformatics workflow locations for Neurotech's NGS analysis and related files can be found in pages 1-9 and 153-161 of (b) (4), and in pages 4-11 and 156-160 of (b) (4). Note that these documents were previously provided in Neurotech response to IR #21

Reviewer Assessment

The Applicant will not be using (b) (4) as part of their manufacturing process nor in the release of (b) (4). Thus, product-specific validation on their (b) (4) method may not be required.

Table 3: (b) (4) Document Designation and Location in BMF (b) (4)

October 4, 2024, Document Designation	LoA Document Designation	(b) (4) Master File (b) (4)
(b) (4)		

Appendix

Table 5: Interactions with the Applicant and additional files reviewed from MF (b) (4).

File Names	Source	Description
bioreliance-ngs-true-hit-assessment.pdf	BI IR #1 Sent: 08/26/2024? Received: 9/4/2024	Description of what constitutes a 'true' hit
ah42sz-706520gmp-bsv-rd1.pdf	BI IR #2 Sent: 10/04/2024 Received: 10/11/2024	Verification testing naïve medium (Endo SFM)
ah42sz-706520gmp-bsv-rd2.pdf	BI IR #2 Sent: 10/04/2024 Received: 10/11/2024	Verification testing for NT-501 spent medium
ah42sz-706520gmp-bsv-rd3.pdf	BI IR #2 Sent: 10/04/2024 Received: 10/11/2024	Verification testing for NT-501 drug substance (cell pellet)
rna-qc-metadata-v0-2.xlw	BI IR #3 Sent: 10/31/2024 Received: 11/8/2024	Sequencing QC metrics
LoA Neurotech Pharmaceuticals, Inc.	BLA	Authorize access for MF 3493
bioreliance-vsr-706520-series.pdf	MF3493/SN4	Validation method
Procedures-analyticalanalytical-procedures-oprd2039.pdf	MF3493/SN4	NGS methodology/bioinformatics
analyticalanalytical-procedures-oprd2040.pdf	MF3493/SN35	NGS methodology/bioinformatics
Validation-validation-of-analytical-procedures-ngs.pdf	MF3493/SN7	NGS methodology/bioinformatics
ts706520gmp-bsv.pdf		Technical Specification for Assay Performance for Project AH42SZ.706520GMP