Food & Drug Administration
Silver Spring, MD 20993

**DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO**

**To:** The file: STN 125730/0

**From:**

| Reviewer | Role | Date finalized | Stamp | Supervisor | Stamp |
|---|---|---|---|---|---|
| Most Nahid Parvin, PhD. | Lead Reviewer | 11/24/2020 | | Muhammad Shahabuddin, PhD. | |
| Simleen Kaur, MS. | Reviewer | 09/22/2020 | | James Kenney, DSc. | |

**Through:** Maryna Eichelberger PhD.
Division Director, DBSQC

**Applicant:** Stratatech, a Mallinckrodt Company

**Subject:** Review of Analytical Methods used for StrataGraft® (Allogeneic Keratinocyte Cell Line (NIKS), seeded on Rat Collagen conditioned with Human Dermal Fibroblasts) Drug Product Lot Release

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**Recommendation:** Approval

**Summary:**

The following analytical methods used for lot release of StrataGraft Drug Product (DP) and the associated analytic method validations or qualifications, were reviewed:

1. (b) (4) for DP (M. Nahid Parvin)
2. Mycoplasma for DP (Simleen Kaur)
3. Endotoxin for DP (Simleen Kaur)
4. Sterility for DP (Simleen Kaur)

**Conclusion:**

The analytical methods and their validations and/or qualifications reviewed for the StrataGraft drug product were found to be adequate for their intended use.

**Documents Reviewed:**

This is an electronic submission. Information submitted and reviewed includes:

- 1.2 Cover letter, dated June 05, 2020
- 2.2. Introduction
- 2.3.P. Drug Product
- 3.2.P.5.2. Analytical Procedures
  - SOP QC-0425 (b) (4) method for StrataGraft skin tissue
  - SOP QC-0471 StrataGraft sampling plan -100 $cm^2$ rectangular tissue
  - 3.2.P.5.6- Analytical Procedures- Mycoplasma
  - 3.2.P.5.7- Analytical Procedures- Endotoxin
  - 3.2.P.5.8- Analytical Procedures- Sterility
- 3.2.P.5.3. Validation of Analytical Procedures
  - Test Validation Report VALREP.002 Method Validation Report for (b) (4) method for StrataGraft skin tissue
  - 3.2.P.5.3.6- Validation of Analytical Procedures- Mycoplasma
  - 3.2.P.5.3.7- Validation of Analytical Procedures- Endotoxin
  - 3.2.P.5.3.8- Validation of Analytical Procedures- Sterility
- 3.2.P.5.4. Batch Analysis
- 3.2.P.5.6. Justifications of Specifications
- 3.2.P.6. Reference Standards or Materials
- 3.2.R.2. Method Validation and Verification report
- 125730/0.4(Amendment)-Recd 07/22/2020-DATS#906849
- 125730/0.9 (Amendment)-Recd 09/02/2020-DATS#917440
- 125730/0.22(Amendment)-Recd 10/29/2020-DATS#930431
- 125730/0.27(Amendment)-Recd 11/20/2020-DATS#935409

**Background:**

Stratatech submitted an original BLA application and requested priority review under section 351(a) of the Public Health Service (PHS) Act for StrataGraft skin tissue on June 5, 2020. The proposed indication is to promote durable wound closure and regenerative healing in the treatment of adult patients with (b) (4) thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated deep partial-thickness (DPT) burns.

StrataGraft skin tissue is a human, bioengineered, regenerative skin construct consisting of an epidermal layer of viable, fully stratified, allogeneic human NIKS® keratinocytes growing on a dermal layer composed of viable human dermal fibroblasts (NHDF) embedded in a collagen-rich matrix. The skin tissue is contained in a 100 $cm^2$ tissue insert with a porous polycarbonate membrane at its base, housed within a (b) (4) product dish, which is heat-sealed in a laminated foil pouch. The final product is supplied with an empty sterile (b) (4) Hold Dish and 15 mL of Hold Solution, which are used to prepare the tissue for surgical application.

The active components of StrataGraft tissue include the viable NIKS and NHDF cells, which have been proposed to produce and release a variety of wound healing factors that are thought to promote wound healing and tissue regeneration. The manufacture of StrataGraft skin tissue is a continuous process which does not allow a hold period and occurs over (b) (4) . Thereby the drug substance is purely notional and defined as the mature skin tissue at the end of the culture steps. StrataGraft skin tissue is manufactured at Stratatech Corporation, 535 Science Drive, Madison, WI. The brief manufacturing process of StrataGraft skin tissue as follows: (b) (4) At the end of the process (b) (4), the mature skin tissues are cryopreserved, packaged and stored at -70 to -90°C.

In this review memo, the analytical method and validation and/or qualification for determination of (b) (4) , mycoplasma, endotoxin and sterility for DP is reviewed.

**1. Determination of (b) (4) : (Drug Product) (M. Nahid Parvin)**

**Introduction**

Analytical method explained in Section 3.2.P.5.2. is a (b) (4) for quantitation of (b) (4) by StrataGraft skin tissue drug product. This method involves sampling plan from StrataGraft tissue

as per SOP QC-0471 and testing the (b) (4) for determination of (b) (4) using the (b) (4) as per SOP QC-0425.

**Review of Method:**

(b) (4)

(b) (4)

**Conclusion:** Assay method is adequately described.

**Review of Method Validation:**

Method validation was performed according to a method validation protocol (MVPRO.002) and is documented in method validation report VALREP.002. Validation parameters specificity, accuracy, precision, linearity, range, robustness and stability indicating characteristics were evaluated.

The validation was performed with 3 lots of StrataGraft tissue (lot# (b) (4) ) and one tissue was tested from each lot. (b) (4)

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

(b) (4)

**Information Request and Review:**

The following information request was submitted to the sponsor on Oct 23, 2020. The response was received on Oct 29, 2020.

**CBER IR-1:** Information request for STN 125730/0 StrataGraft skin tissue original BLA regarding the analytical procedure for determination of (b) (4):

1) (b) (4) from (b) (4) are used to determine (b) (4) by StrataGraft skin tissue. It is stated in the validation report (VALREP.002) that procedures are being developed to qualify every new lot of the (b) (4) for its suitability before using in release testing. Please provide the qualification procedure for new (b) (4) lots. If the procedure is not finalized yet, please provide the date it will be finalized. A response is requested by 29 October 2020.

**Sponsor Response:**

Each (b) (4) will be qualified prior to release for use. (b) (4) controls are used as a sample during the qualification of each new lot of (b) (4) received and are tested per instruction described in SOP-QC-0425 section 7.4. The (b) (4) are considered suitable for use if the values of the controls are within expected values listed on the CoA (see representative (b) (4) Control CoA).

**Reviewer Response:**

The following information request was submitted on Nov 6, 2020 for further clarification and the response was received on Nov 20, 2020.

**CBER IR-2:** In your response dated October 29, 2020, you indicate using SOP-QC-0425 to qualify each (b) (4) lot prior to use in testing samples. We have the following concerns:

1) Your response indicates you consider (b) (4) acceptable when the control values are within the expected values listed on the CoA. Because of site-specific test conditions, it is recommended you establish your own acceptance criteria for the (b) (4) control concentrations. Please provide data from at least (b) (4) independent assays that support the acceptance criteria you are using in your QC laboratory.

2) We have some concern regarding the (b) (4) variability within each lot and recommend you include a positive (b) (4) control (preferable at (b) (4) concentrations) in each test. Criteria for the results of the positive control lot(s) should be established to demonstrate the assay run is acceptable.

3) The (b) (4) control lot provided by (b) (4) is likely to be replaced at some point. It is recommended to calibrate the new (b) (4) control lot with previous (b) (4) control lot before using it.

**Sponsor Response:**

1) Data from (b) (4) independent assays of the (b) (4) controls at the (b) (4) control concentrations are provided in Table 1. The results obtained from the study conducted at Stratatech demonstrate that the results obtained from the vendor (b) (4) qualification are similar to those provided on the vendor's Certificate of Analysis (CoA). Based on the data collected, Stratatech will implement the following acceptance criteria for the vendor (b) (4) qualification: (b) (4)

2) In alignment with the Agency's recommendation, Stratatech will include a positive (b) (4) control at (b) (4) concentrations in each test. An updated 3.2.P.5.2–(b) (4) is provided with the addition of the positive (b) (4) controls.

**Reviewer Response:**

The sponsor established a range for the controls that will be used as acceptance criteria for new (b) (4) lot qualification and for each test's system suitability. Although the range of the assay is (b) (4), the standard curve in each assay spans (b) (4). Per SOP QC-0425, the (b) (4) controls ((b) (4) concentrations) are (b) (4) as per vendor's instruction and (b) (4) samples are tested.

The positive controls used in the assay and the acceptance criteria are therefore acceptable.

**Reviewer comments and conclusion:**

The data submitted for review demonstrate specificity, accuracy, precision, linearity, range and robustness of the (b) (4). In addition, the assay was shown to be stability indicating. The (b) (4) to determine (b) (4) from StrataGraft tissue is therefore acceptable and appropriate for intended use.

## 2. Mycoplasma (Drug Product) (Simleen Kaur)

**Mycoplasma Test Qualification:**

Mycoplasma testing is performed by (b) (4) methods. (b) (4)

**Culture Method Qualification**

Stratatech qualified final product containing cells for mycoplasma test to demonstrate the method is suitable under the actual conditions of use by testing via (b) (4)

The description of the qualification that follows takes into consideration the response to the IR.

(b) (4)

(b) (4)

The results of the (b) (4) method for xx DP matrix met the validity criteria. That is: (b) (4)

The results indicated there is no product inhibition on mycoplasma growth.

(b) (4) **Method Qualification**

Stratatech qualified drug product for mycoplasma test to demonstrate the method is suitable under the actual conditions of use. Testing via (b) (4) assay was performed using three lots of final product containing cells (i.e., (b) (4)) and (b) (4) mycoplasma strains, (b) (4).

(b) (4)

(b) (4)

The results of (b) (4) met the validity criteria. That is, (b) (4) The (b) (4) demonstrate the xx DP matrix does not interfere with the detection of mycoplasma.

(b) (4) methods were performed, and the results were compliant with (b) (4), thus demonstrating the methods are suitable under the actual conditions of use.

**Information Request and Review**

The following question was sent in an IR to the sponsor on July 9, 2020 and response was received on July 22, 2020.

a. (b) (4), refers to a list of different (b) (4) for (b) (4) test method. Please provide the composition of (b) (4) used in (b) (4) method to verify it is in accordance with (b) (4) recommendations.

   Review of the Response
   A detailed description of (b) (4) composition was provided and found to follow (b) (4) requirements. The response was found acceptable.

**3. Endotoxin (Drug Product) (Simleen Kaur)**

(b) (4) **-Bacterial Endotoxin Test ((b) (4)-BET) Qualification**

(b) (4) -BET utilizes (b) (4)

Stratatech qualified their (b) (4)-BET by testing three lots of drug product (i.e., (b) (4)) to demonstrate their method is suitable under the actual conditions of use in accordance with (b) (4)

(b) (4)

Stratatech submitted bacterial endotoxin concentration results of several lots of drug product and all were found to be within their proposed release specification of (b) (4). After review of (b) (4)-BET test, this reviewer concludes the test method was performed and was compliant with (b) (4).

**4. Sterility (Drug Product) (Simleen Kaur)**

**Sterility Test Qualification**

Since StrataGraft® manufacturing is a continuous process, sterility testing is performed at several stages (i.e., (b) (4) final tissue drug product). Sterility testing for all these stages were reviewed.

Stratatech qualified (b) (4) final tissue drug product using the (b) (4) method and (b) (4) using (b) (4) method by performing (b) (4) study to demonstrate the methods are suitable under the actual conditions of use in accordance with (b) (4). The (b) (4) method is designed to (b) (4) The (b) (4) method is designed to (b) (4). The methods are described below, together with the tests that were performed to demonstrate suitability of the test method.

The tests were performed using (b) (4) indicator microorganisms (i.e., (b) (4)) and (b) (4) environmental isolate (i.e., (b) (4)). The original submission did not include (b) (4)

(b) (4) as well as lot numbers for test material used in the qualification studies, therefore, IRs were sent on July 9 and August 18, 2020, respectively, requesting the missing information. The description of the qualification that follows takes into consideration the response to the IR.

(b) (4)

**Information Request and Review**

The following questions were sent in an IR to the sponsor on July 9 and August 18, 2020 and responses were received on July 22 and September 2, 2020, respectively.

a. Sterility test qualification studies submitted under section 3.2.P.5.3 have test results of microorganisms after the (b) (4) . However, additional

information is needed; please submit the initial (b) (4) results for all microorganisms to ensure inoculum levels were below (b) (4) .

Review of the Response
Stratatech submitted initial (b) (4) results for all microorganisms for (b) (4) methods. The response was found acceptable.

b. For sterility test qualification studies submitted under section 3.2.P.5.3, please provide lot numbers of test samples (i.e., (b) (4) final tissue drug product) used in the study.

Review of the Response
Stratatech submitted lot numbers for test samples used in the qualification studies. The response was found acceptable.

**Conclusion:**

After a thorough review of the information submitted in this BLA, this reviewer finds that the mycoplasma, endotoxin and sterility test methods were qualified in accordance with (b) (4) , respectively, and demonstrated to be suitable under the actual conditions of use. Therefore, this reviewer finds these methods acceptable for their intended purpose and recommends their approval.