CBER CMC BLA Review Memorandum

BLA STN 125730

Product name: STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat)

Takele Argaw (TA), DVM | Biologist | CBER/OTAT/DCGT/GTIB
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1. BLA#: STN 125730

2. APPPLICANT NAME AND LICENSE NUMBER

Stratatech Corporation
License Number: 2144 (pending)

3. PRODUCT NAME/PRODUCT TYPE

Proper name: allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat
Proprietary name: STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen- dsat)
Product title: STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen- dsat), for topical use
Product Type: tissue engineered epidermal allograft

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Pharmacological category: tissue engineered epidermal allograft
b. Dosage form: an off-white rectangular sheet of approximately 100 cm^2 (approximately 8 cm by 12.5 cm), consisting of a viable, bioengineered, allogeneic cellularized scaffold product derived from human keratinocytes grown on gelled collagen containing human dermal fibroblasts.
c. Strength/Potency: The number of tissues applied will vary depending on the size of the wound bed.
d. Route of administration: Topical application
e. Indication(s): STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen – dsat) is a tissue engineered epidermal allograft indicated for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns).

5. MAJOR MILESTONES

Initial Modules Received	March 30, 2020
Module 3 Received	June 5, 2020
Application Filed	August 4, 2020
Mid-Cycle Communication	October 1, 2020
Late-Cycle Communication	November 12, 2020
Advisory Committee Meeting	None held
Inspections	BIMO: FEI 3017215122 Michael Schurr, NC 9/4/20 – 9/14/20 Pre-License: May 3-7, 2021
PDUFA Action Date:	February 4, 2021

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Steven R. Bauer, OTAT/DCGT/CTTB	**Environmental Analysis (1.12.14)** **Labeling (1.14)** **3.2.S DRUG SUBSTANCE**; 3.2.S.1 General Information 3.2.S.1.1 Nomenclature; 3.2.S.1.2 Structure ; 3.2.S.1.3 General Properties 3.2.S.2 Manufacture 3.2.S.2.1 Manufacturer(s) 3.2.S.2.2 Description of Manufacturing Process and Process Controls 3.2.S.2.3 Control of Materials 3.2.S.2.3-1 NHDF cell banks 3.2.S.2.3-2 NIKS cell banks 3.2.S.2.5 Process Validation and/or Evaluation 3.2.S.2.6 Manufacturing Process Development 3.2.S.3 Characterization 3.2.S.3.1 Elucidation of Structure and other Characteristics 3.2.S.3.2 Impurities 3.2.S.4 Control of Drug Substance 3.2.S.4.1 Specification 3.2.S.4.2 Analytical Procedures 3.2.S.4.3 Validation of Analytical Procedures 3.2.S.4.4 Batch Analyses 3.2.S.4.5 Justification of Specification 3.2.S.5 Reference Standards or Materials 3.2.S.6 Container Closure System 3.2.S.7 Stability 3.2.S.7.1 Stability Summary and Conclusions 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment 3.2.S.7.3 Stability Data **3.2.P DRUG PRODUCT STRATAGRAFT** 3.2.P.1 Description and Composition of the Drug Product 3.2.P.2 Pharmaceutical Development 3.2.P.2.1 Components of the Drug Product 3.2.P.2.1.1 Drug Substance 3.2.P.2.1.2 Excipients 3.2.P.2.2 Drug Product 3.2.P.2.2.1 Formulation Development 3.2.P.2.2.2 Overages 3.2.P.2.2.3 Physicochemical and Biological Properties 3.2.P.2.3 Manufacturing Process Development 3.2.P.3 Manufacture 3.2.P.3.1 Manufacturer(s) 3.2.P.3.2 Batch Formula 3.2.P.3.3 Description of Manufacturing Process and Process Controls 3.2.P.3.4 Controls of Critical Steps and Intermediates 3.2.P.3.5 Process Validation and/or Evaluation 3.2.P.5 Control of Drug Product 3.2.P.5.1 Specification(s) 3.2.P.5.2 Analytical Procedures 3.2.P.5.2 -1 to - 5 3.2.P.5.2 -6 to -8 mycoplasma, endotoxin, sterility

	3.2.P.5.2 -9 Container Closure 3.2.P.5.3 Validation of Analytical Procedures 3.2.P.5.3 -1 to - 5 3.2.P.5.2 -6 to -8 mycoplasma, endotoxin, sterility 3.2.P.5.4 Batch Analyses 3.2.P.5.5 Characterization of Impurities 3.2.P.5.6 Justification of Specification(s) 3.2.P.6 Reference Standards or Materials 3.2.P.7 Container Closure System 3.2.P.8 Stability 3.2.P.8.1 Stability Summary and Conclusion: Hold Solution 3.2.P.8.1 Stability Summary and Conclusion: 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment 3.2.R.3 Executed Batch Record 3.2.R.4 Xenotransplantation Exemption Justification 1.1. Culture History of (b) (4) Cells Culture history of the (b) (4) line 1.2. Characterization of the (b) (4) Master Cell Bank 1.3. Characterization of the (b) (4) Murine Feeder Cells 1.4. Characterization of the NIKS MCB and WCB 1.4.1. Additional Adventitious Agent Testing of NIKS Keratinocytes 3.2.R.5 Growth Factor Secretion 3.2.R.6 Glycerol Safety Risk Assessment
Takele Argaw, OTAT/DCGT/GTIB	3.2.S.2.3-1 NHDF cell banks; 3.2.A.2 Adventitious Agents Safety Evaluation 3.2.R.4 Xenotransplantation Exemption Justification/Virology
John (Terrig) Thomas, OTAT/DCGT/CTTB	3.2.P.5.1 Specification(s); 3.2.P.5.2 Analytical Procedures; 3.2.P.5.2 -1 to – 5; 3.2.R.2 Method Validation and Verification Reports appearance, histology, viability, barrier function, (b) (4) / Analytical assay validation
Laura Ricles, OTAT/DCGT/CTB	3.2.P.4.1 Specifications: 3.2.P.5.2 -9 Container Closure: 3.2.P.7 Container Closure System; 3.2.P.8.1 Stability Summary and Conclusion: Hold Solution; 3.2.P.8.3 Stability Data: Hold Solution; 3.2.A.3 Excipients; 3.2.R.1 Certificates of Analysis; 3.2.R.7 (b) (4) /Product specifications, packaging
John Dennis, CBER/OD/DVM (consult)	3.2.S.2.3-2 NIKS cell banks 3.2.R.4 Xenotransplantation Exemption Justification/ Veterinary and xenotransplantation
Dan (Kelly) Wang CBER/OTAT/DHT (consult)	1. Section 3.2.S.2.3-1 Control of Materials – NHDF Cell Banks (b) (4) Media 2. Section 3.2.S.2.3-2 Control of Materials – NIKS Cell Banks (b) (4) Media

Most Nahid Parvin CBER/OCBQ/DBSQC (consult)	3.2.R.2 Method Validation and Verification Reports (b) (4) 3.2.P.5.2. Analytical Procedures (b) (4) – 3.2.P.5.4. Batch Analysis – 3.2.P.5.6. Justifications of Specifications – 3.2.P.6. Reference Standards or Materials
Simleen Kaur, MS. CBER/OCBQ/DBSQC (consult)	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.R.2 Method Validation and Verification Reports/Mycoplasma/Endotoxin/Sterility – 3.2.P.5.4. Batch Analysis – 3.2.P.5.6. Justifications of Specifications – 3.2.P.6. Reference Standards or Materials

7. INTER-CENTER CONSULTS REQUESTED

Reviewer/Affiliation	Section/Topic	In agreement with consult recommendations
Berk Oktem CDRH/OSEL/DBCMS	3.2.R.7 E & L; extractables and leachables	Yes
Tek Lamicchane CDRH/OHT4/THT4B4	3.2.S.2.3-5 Control of Materials Collagen viral inactivation	Yes
John Azeke CDRH/OPEQ/OHTIV/DHTIVB	3.2.P.5.2 Analytical Procedures Barrier Function	Yes

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
3/30/3030	125730/0000	BLA rolling submission initiated Modules 1, 2, 4, and 5 excluding Module 2.3
6/5/2020	125730/0002	Module 3 and 2.3; application complete
6/19/2020	125730/0003	Response to IR #1
6/7/2020	125730/0004	Response to IR #2
7/22/2020	125730/0005	Response to IRs #3 and 4
7/22/2020	e-mail	Response to IR #6
7/28/2020	125730/0006	Response to IR #5
8/3/2020	125730/0007	Response to APLB suffix request
8/21/2020	125730/0008	Response to IRs #7 and 8
8/25/202	125730/0009	Response to IR #11
9/2/2020	125730/0010	Responses to IR #9 and 10
9/4/2020	125730/0011	Response to IR #12
9/10/2020	125730/0012	Clinical Study Report (CSR) Addendum

9/17/2020	125730/0013	Response to IR #16
9/18/2020	125730/0014	Response to IR #13
9/21/2020	125730/0015	Response to IR #18
9/22/2020	125730/0016	Response to IR #15 Q 1 and 2
9/28/2020	125730/0017	Responses to IRs #9, 14, 17, 20, 21
9/30/2020	125730/0018	Responses to IRs #14 and 22
10/2/2020	125730/0019	Day 120 Safety Update, Response to IR #15
10/9/2020	125730/0020	Response to IR #23
10/14/2020	125730/0021	Response to IR #24
10/15/202	e-mail	Response to IR #25
10/23/2020	125730/0022	Applicant Mid Cycle meeting minutes
10/29/2020	125730/0023	Responses to IRs #23, 26, 27
10/20/2020	125730/0024	Responses to IRs #14, 22, 28
11/6/2020	125730/0025	Responses to IRs #21, 31
11/12/2020	125730/0026	Response to IR #29
11/18/2020	125730/0027	Response to IRs #34, 35
11/20/2020	125730/0028	Response to IRs #24, 33
11/30/2020	125730/0029	Response to IRs #30, 32
12/23/2020	125730/0030	Response to IR#15, histology validation and cell bank purity (Mid-Cycle issues)
1/6/2021	125730/0031	Response to IR # 36
1/8/2021	125730/0032	Updated labeling
1/11/2021	125730/0033	Response to IR#37
1/25/2021	125730/0034	Response to IR#38, labeling update, archiving for xenotransplantation
2/5/2021	125730/0035	Updated PI
2/8/2021	125730/0036	Response to IR#39
2/10/2021	125730/0037	Updated labeling
2/12/2021	125730/0038	LOA for MF (b) (4)
2/15/2021	125730/0039	Corrected carton label and xenotransplantation information
2/16/21	125730/40	New (b) (4) for virus detection in collagen
3/3/2021	125730/41	LOA for MF (b) (4)
3/9/2021	125730/42	Package labeling updates
3/19/2021	125730/43	PI updates
3/29/2021	125730/44	Package labeling updates
3/31/2021	125730/45	Validation report for (b) (4) viral test
4/6/2021	125730/46	Finalized PI and Patient Information Sheet
4/30/2021	125730/47	Finalized packaging labels
5/4/2021	125730/48	Change in sponsor contact
5/20/2021	125730/49	USPI and Patient Information Sheet corrections
5/25/2021	125730/50	Package labeling correction
5/27/2021	125730/51	Patient Information Sheet correction
6/4/2021	125730/52	PMR/PMC responses
6/9/2021	125730/53	PMR proposal
6/10/21	125730/54	Final PMR agreement
6/10/21	125730/55	Corrected Carton Label
6/11/2021	125730/56	Final PMC commitment

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
IND 10113	Stratatech	All information	N/A	Active IND
DMF (b) (4)	(b) (4)	Hold Solution Bottle	yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Hold Solution Bottle Cap	yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Hold Solution Bottle Cap	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Hold Solution Bottle Cap	Yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Product Dish	yes	No DMF review required, information pertinent to container closure is provided in the BLA
DMF (b) (4)	(b) (4)	Virus testing	yes	Reviewed for virus assay validation by (b) (4) for 3.2.A.2 Adventitious Agents Safety Evaluation
DMF (b) (4)	(b) (4)	Viral testing	Yes	Reviewed for virus assay validation by (b) (4) for 3.2.A.2 Adventitious Agents Safety Evaluation
DMF (b) (4)	(b) (4)	Viral testing	Yes	Reviewed for virus assay validation by (b) (4) for 3.2.A.2 Adventitious Agents Safety Evaluation

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Product Description: STRATAGRAFT is an off-white rectangular sheet of approximately 100 cm^2 (approximately 8 cm by 12.5 cm), consisting of a viable, tissue engineered epidermal allograft derived from keratinocytes grown on gelled collagen containing dermal fibroblasts. The final

product has mechanical properties that allow it to undergo meshing before application. It is manufactured in a continuous process encompassing (b) (4) from initiation of cell culture, formation of a dermal equivalent consisting of human dermal fibroblasts mixed with rat-tail collagen type I, seeding of NIKS keratinocytes cells over the dermal equivalent, maturation and development of a bilayered skin-like tissue construct in a custom tissue culture apparatus, to final packaging and cryopreservation in a novel tissue tray sealed in a foil package. The product has a twelve-month shelf-life under cryopreservation. Each of the packaged constructs is a single unit and the process is validated to manufacture at a (b) (4) scale.

STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat) is an allogeneic cellularized scaffold product indicated for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns).

Regulatory History: STRATAGRAFT is under Stratatech's Investigational New Drug application (IND)10113, first submitted to CBER in 2001. A Biologics License Application (BLA) for this product was submitted as a rolling application on March 30, 2020 and completed June 5, 2020. It was granted Orphan Drug designation in 2012 (ODD #12-3653) for the treatment of hospitalized patients with complex skin defects resulting from partial and full thickness skin burns requiring excision and grafting. It was granted Regenerative Medicine Advanced Therapy (RMAT) designation on July 6, 2017 for the allogeneic keratinocyte cell line (NIKS) seeded on rat collagen conditioned with human dermal fibroblasts for the treatment of patients with acute burns. A breakthrough designation request was denied on April 23, 2014.

Ever since the original IND was submitted in 2001, STRATAGRAFT has been designated a xenotransplantation product because the NIKS keratinocyte cell line was originally cultured in the presence of the (b) (4) cells. In BLA 125730, the Applicant included a request for exemption from the FDA xenotransplantation requirements. In a letter (December 18, 2020), the Applicant was informed that this request was denied and FDA clarified requirements for appropriate xenotransplantation policy compliance.

The Applicant also submitted a Material Threat Medical Countermeasure Priority Review Voucher as part of the BLA. FDA determined that the request Denial of this request will be communicated in the package decision letter to the Applicant.

Xenotransplantation Risk Analysis: Information submitted during review demonstrates that DNA from the allogenic cell lines normal human dermal fibroblasts (NHDF) and NIKS is not detectable at 3 months after product placement on wound sites. This limits the time of exposure to the product, likely reducing exposure-related risk to this time. Potential xenotransplantation-related risks for this product are likely lower than current xenotransplantation cultured epidermal autograft product Epicel, marketed under an HDE. Epicel uses mouse 3T3 cells during manufacturing, whereas STRATAGRAFT manufacturing no longer uses mouse feeder cells. There have been no reported public xenotransplantation health concerns with Epicel and none have been reported for STRATAGRAFT, which has been used in clinical trials for more than 15 years. Based on the extensive cell-line testing for xeno-related viruses (including (b) (4)), lack of detectable mouse DNA in the product, and lack of clinical concerns regarding xeno-related adverse events, STRATAGRAFT seems to present less of a risk than Epicel.

Also, due to the xenotransplantation-related nature of STRATAGRAFT, the pharmacovigilance plan includes expedited reporting for adverse events possibly related to xenotransplantation. Taken together, the xenotransplantation risks are acceptable and do not preclude approval of this product.

Process Development: The STRATAGRAFT manufacturing process has undergone (b) (4) significant developmental stages. (b) (4)

(b) (4)

Manufacturing Summary: Manufacturing control strategies include testing and characterization of the NHDF and NIKS working cell banks (WCBs), extensive process performance qualification (PPQ) studies, appropriate in process (b) (4) for the phases of (b) (4) final cryopreservation of the construct), and appropriate final product testing of drug product thawed after cryopreservation. The final product tests and release criteria are appropriate and satisfy regulatory requirements for identity, purity, and potency. Unique product characterization assays include sacrifice of individual units for testing and use of biopsies for analytical assays. Assessment of viability is made using the (b) (4) assay to measure (b) (4) of the tissue. Assessment of (b) (4) from biopsy samples is used to demonstrate a relevant biological activity. The release criteria for (b) (4) align with the proposed mechanism of actions relevant to healing of thermal burns. Another unique assessment of product quality is measurement of barrier function that indicates formation of an outer skin-like cornified epithelium resistant to moisture exchange. Stability studies (in storage and shipping) are appropriate, and support product expiration dating. The process is well controlled and has demonstrated ability to produce drug product (DP) of acceptable quality. These conclusions support approval of the BLA.

Consult Reviews: CDRH colleagues reviewed: 1) information on extractables and leachables associated with the novel tissue tray, hold dish and other elements of product packaging; 2) information on manufacturing, characterization and viral clearance studies of the rat-tail collagen type I; and 3) information on a device ((b) (4)) and its performance) when used during product characterization for measurement of barrier function. A CBER OTAT/DHT colleague conducted a review of available donor and screening information and concluded that because the cell bank was established prior to May of 2005, donor eligibility requirements in 21 CFR part 1271 are not applicable. However, the available information is adequate to support licensure of the product.

Review Issues:

Major deficiency: There was inadequate information on performance and validation by the CROs that perform adventitious agent testing. Also, there was inadequate information on viral clearance during manufacturing of the collagen. Several IRs were issued and there was discussion about this topic at the Mid Cycle and Late Cycle meetings to address these issues. Due to the lack of Master Files for some of the adventitious virus testing by CROs, FDA accepted viral validation reports by e-mail from vendors to support the Applicant's BLA. These documents were reviewed and archived in an FDA electronic database. Subsequently, appropriate Master File and LOAs were submitted to the BLA and cover the information previously reviewed in e-mail submissions. Most of the information pertaining to Module 3 section 3.2.A. 2 is complete and acceptable. However, there are remaining questions regarding viral clearance during manufacturing of rat tail collagen.

The rat tail collagen type I presents a potential, but small risk of transmission of adventitious virus which could result in a serious adverse event (SAE). Currently, the Sponsor is deficient in their viral clearance study by only achieving a (b) (4) clearance for two of three model viruses (> 6 log 10 is

FDA's current recommendation). A third model virus ((b) (4)) did not demonstrate any clearance. Overall, this lack will not be considered sufficient to warrant a CR since this product which received an RMAT designation addresses an unmet medical need and the Applicant has other controls in place to mitigate the risk of rat-specific viral transmission, including monitoring and pathogenic testing of the closed rat colonies, lot release adventitious agent testing of the collagen, enhanced pharmacovigilance monitoring, and no reported adverse events related to rat-specific viral infection. To further evaluate the potential of an unexpected serious risk, the Applicant will be required to conduct a viral clearance study as a Title IX PMR. This would demonstrate clearance of model viruses Parainfluenza virus type 3 (PI3), Pseudorabies virus (PRV) and Murine Minute Virus (MMV). The Sponsor would need to show a clearance level of >6 log 10 for all viruses.

PMR

In Amendment 55, Sequence 54 Stratatech agrees to conduct a postmarketing study to demonstrate clearance of model viruses Parainfluenza virus type 3 (PI3), Pseudorabies virus (PRV) and Murine Minute Virus (MMV) in rat tail collagen type 1. The clearance level of >6 log 10 will be demonstrated for all viruses.

Draft protocol to FDA: Sep 30, 2021
Final protocol to FDA: Nov 30, 2021
Study completion: Mar 31, 2022
Final report: Apr 30, 2022

Minor Deficiencies: The cell banks are characterized for (b) (4) and ability to produce product that meets quality attributes. However, the characterization lacks other meaningful measures of unique cell identity or function that would be stability-indicating and predictive of acceptable manufacturing capability. Also, the genetic identity testing is based on a method that will not detect contaminating cells. These issues were discussed with the sponsor in the Late Cycle meeting and via IR#28 and the sponsor proposed that they respond in two PMCs. An e-mail requesting an update on these issues was sent to the Applicant on 2/3/2021. The e-mail addressed the following: Current cell bank identity tests are not adequate to detect potential cell-line contamination or to assess phenotypic stability of NHDF and NIKS cells banks. The current (b) (4)-based identity test for the NHDF and NIKS cell banks does not allow for detection of contamination by other human cell lines. Contamination of these cell sources with unintended human cells could lead to inadequate product quality. In order to reduce the risk of untended human cellular contamination, we request that you adopt a method that can confirm the identity of your cell banks and detect the presence of (b) (4). The method should be validated and the sensitivity of the assay to detect (b) (4) should be established as part of this validation. Also, you do not have cell-marker identity tests suitable for assessing phenotypic stability which is important for maintaining product quality. In order to better ensure cell bank stability, we request that you identify suitable cell markers and develop identity tests that can serve as suitable identity tests for monitoring stability and function of your cell banks.

PMCs: In Amendment 56, Sequence 55 on 6/11/2021 Stratatech committed to perform two PMC studies

PMC #1: Stratatech commits to implement a (b) (4)-based method that can confirm the identity of the NIKS and NHDF cell banks and detect the presence of (b) (4). The method will be validated and the sensitivity of the assay to detect (b) (4) will be established as part of this validation.

A Prior Approval Supplement will be submitted by April 30, 2022.

PMC #2: Stratatech commits to develop validated identity tests that will serve for monitoring stability and function of NIKS and NHDF cell banks. When established, these tests will be incorporated as part of on-going stability studies.

A Prior Approval Supplement will be submitted by April 30, 2022

In a telecon on 2/3/2021, the Applicant was informed that due to restrictions on travel during the pandemic, we were unable to conduct an inspection during the current review cycle, and that we were deferring action on the application until an inspection could be completed. The PLI took place May3-7, 2021. No 483 observations were issued.

Conclusions: The PLI confirmed that the product and manufacturing processes are well controlled and capable of producing a consistent 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 PMR and PMCs discussed above.

B. RECOMMENDATION

I. APPROVAL

a. Approval Letter: Stratatech Corporation
510 Charmany Drive, Suite 150
Madison, WI 53719

b. Comparability Protocols N/A

c. Post marketing issues

i. PMR: collagen viral clearance. CBER's SWG discussed and approved this PMR on 1/28/2021.

Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)). We have determined that an analysis of spontaneous postmarketing adverse events reported under section 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of patient exposure to murine (rat) virus and subsequent viral infection, in association with the use of STRATAGRAFT.

Furthermore, the pharmacovigilance system that FDA is required to maintain under section 505(k)(3) of the FDCA is not sufficient to identify this potential for serious risk. Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

We have determined that you are required to conduct the following study as a post-marketing requirement (PMR):

PMR
Conduct a study to assess the risk of adventitious virus by demonstrating clearance of model viruses Parainfluenza virus type 3 (PI3), Pseudorabies virus (PRV) and Murine Minute Virus (MMV) in rat tail collagen type 1. The clearance level of >6 log 10 will be demonstrated for all viruses.

Draft protocol to FDA: Sep 30, 2021
Final protocol to FDA: Nov 30, 2021
Study completion: Mar 31, 2022
Final report: Apr 30, 2022

ii. PMCs
In Amendment 56, Sequence 55 on 6/11/2021 Stratatech committed to perform two PMC studies

PMC #1:
Stratatech commits to implement a (b) (4)-based method that can confirm the identity of the NIKS and NHDF cell banks and detect the presence of (b) (4). The method will be validated and the sensitivity of the assay to detect (b) (4) will be established as part of this validation.

A Prior Approval Supplement will be submitted by April 30, 2022.

PMC #2:
Stratatech commits to develop validated identity tests that will serve for monitoring stability and function of NIKS and NHDF cell banks. When established, these tests will be incorporated as part of on-going stability studies.

A Prior Approval Supplement will be submitted by April 30, 2022

d. Inspectional issues: No 483 observations issued during PLI May 3-7, 2021. No objectionable conditions were noted.

II. COMPLETE RESPONSE (CR)

The BLA will not be subject to CR.

III. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Steven R. Bauer, Chair OTAT/DCGT/CTTB	Concur	
Takele Argaw, OTAT/DCGT/GTIB	Concur	
John (Terrig) Thomas, OTAT/DCGT/CTTB	Concur	
Laura Ricles, OTAT/DCGT/CTB	Concur	
John Dennis, CBER/OD/DVM	Concur	
Most Nahid Parvin CBER/OCBQ/DBSQC	Concur	
Melanie Eacho, Chief CTB OTAT/DCGT/CTB	Concur	Concur
Steven Oh, Deputy Director DCGT OTAT/DCGT	Concur	Concur
Raj Puri, Director DCGT OTAT/DCGT	Concur	Concur

Table of Contents

Table of Figures

Table of Tables

Module 3

MODULE 3 ORGANIZATION

Manufacture of STRATAGRAFT is a (b) (4) drug substance (DS) and drug product (DP). At the pre-BLA meeting, the applicant proposed where CMC information would be presented in the eCTD and FDA agreed to the proposed placement of DS and DP information. Drug substance MODULE 3.2.S describes the (b) (4) process used to manufacture STRATAGRAFT up to the stage (b) (4) prior to cryopreservation and packaging, when no further change in structure and/or function of the product is intended.

The drug product MODULE 3.2.P primarily describes the steps of washing, packaging and cryopreservation, and final release testing that occurs after the packaging of the DP. However, the DS and DP sections overlap due to the continuous manufacturing approach and the nature of the tissue engineered product.

Review comment: due to overlap, many portions of the DP review refer to the corresponding DS section.

Unless otherwise indicated, Tables and Figures in this review **were supplied by the Applicant**.

3.2.S DRUG SUBSTANCE

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

The product is a tissue engineered skin replacement construct. As such it does not have a USAN name. The proprietary name is STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat), for topical use. The proper name is **allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat**.

STRATAGRAFT is a viable, tissue engineered skin construct containing an epidermal layer formed from differentiated NIKS keratinocytes and a dermal equivalent layer formed from differentiated normal human dermal fibroblasts (NHDF) embedded in a collagen gel matrix (rat tail tendon Type I).

(b) (4)

Reviewer Comments: Tissue engineered products are excluded from USAN naming schemes for cell-based products so the proprietary and proper names of this product were based on the nature of the product.

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

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

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT

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

STRATAGRAFT is a rectangular (100 cm^2, 8.5 x 12.5 cm), viable, tissue engineered skin construct containing an epidermal layer formed from differentiated NIKS keratinocytes and a dermal equivalent layer formed from differentiated normal human dermal fibroblasts (NHDF) embedded in a gel matrix originating from rat tail tendon Type I. Product quality is assessed by lot release testing including lack of detectable adventitious agents, sterility, mycoplasma and endotoxin as well as functional characteristics such as viability, barrier function, and (b) (4) . Other pertinent characteristics including ability to undergo physical handling and meshing have also been qualified. STRATAGRAFT 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 cryopreserved in a glycerin-based cryoprotectant and is supplied with an empty sterile (b) (4) Hold Dish and 15 mL of Hold Solution, which are used to thaw and prepare the tissue for surgical application.

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

STRATAGRAFT manufacture is a continuous process with no intermediate holds or stages. Drug substance is designated as the manufacturing stage at which (b) (4) prior to cryopreservation and packaging.

Manufacturing development studies outlined in section 3.2.S.2.6 Manufacturing Process Development and 3.2.P.2.3 Manufacturing Process Development confirm that excipients used in manufacturing and prior to clinical application (Hold Solution) are suitable to maintain the quality attributes of the cultured skin tissue.

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3.2.P.2.1.2 Excipients

Final product formulation is in Cryopreservation Solution (CPS) [(b) (4) containing (b) (4) glycerol], which acts as a cryoprotectant for storage at -70 to -90°C. Glycerol is widespread use in the cryopreservation of human cells and has an acceptable safety profile with low toxicity (see P/T review). (b) (4) is the culture medium used in the manufacture of STRATAGRAFT. (b) (4) is a well-characterized (b) (4) of the CPS. The product is supplied with Hold Solution [(b) (4)] used to thaw STRATAGRAFT for clinical application. Hold Solution is used to thaw and prepare the construct for surgical application. Hold Solution provides (b) (4) immediately prior to clinical use. Product thawed and help for periods of 15 minutes up to 4 hours met lot release specifications for viability and histology. The formulation of the excipients is provided in section 3.2.P.3.2 Batch Formula.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

Formulation Development

Studies presented in sections 3.2.S.2.6 Manufacturing Process Development and 3.2.P.2.3 Manufacturing Process Development evaluated the effect of cryopreservation on key parameters such as (b) (4) .

Initial drug product storage conditions were at (b) (4) although stability was demonstrated for (b) (4) . This did not allow completion of (b) (4) sterility tests before product administration. Cryopreservation studies were conducted to allow sufficient time to compete sterility tests prior to release of drug product, to facilitate adequate supply for commercial use, and to enable product shipment.

Studies that supported development of the CPS are described in Section 3.3 of 3.2.P.2.3 Manufacturing Process Development.

Also, a Hold Solution for thaw of the product immediately prior to clinical use was developed. The Hold Solution is provided with a sterilized Hold Dish for thawing the frozen product. The Hold Dish is identical to the product packaging Product Dish.

Initially, post-thaw hold studies (b) (4) .

Tissues (b) (4) met lot release specifications for all tissues held from 15 minutes to 4 hours after being thawed at room temperature. To avoid having to supplement (b) (4) , studies to asses use of a commercially available (b) (4) were done and showed that all tissues met lot release specifications for viability and histology after the post thaw hold periods of 15 minutes up to 4 hours. Results are in section 3.2.P.2.3 Manufacturing Process Development.

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3.2.P.2.2.2 Overages

- Not applicable to this product

3.2.P.2.2.3 Physicochemical and Biological Properties

When formulated, the dermal equivalent (DE) consists of input murine type I collagen and normal human dermal fibroblasts (NHDF). Extracellular matrix (ECM) composition of mature product was assessed for (b) (4) during product manufacture. The studies show that the DE undergoes significant changes during the manufacturing process, through elaboration of human ECM molecules from NIKS keratinocytes and NHDF. (b) (4) confirmed the biosynthesis of human type I collagen.

Additionally, synthesis of (b) (4) support the organization of a mature type I collagen network by the cellular components of STRATAGRAFT. Biosynthesis and appropriate localization of (b) (4) was indicative of the presence of a dermal microfibrillar network. Finally, the synthesis and appropriate localization of (b) (4) demonstrate that STRATAGRAFT is likely to assemble basement membrane and dermal-epidermal junctions. The functional roles of these ECM proteins in signaling and structural activities of dermal tissue have been reported in literature.

Study Summary

(b) (4) studies show:

(b) (4)

The data suggest the developing Dermal Equivalent is transformed by the production and assembly of many of the major structural and functional ECM elements of human skin.

The modification and reorganization of the ECM parallels the changes in the overall DE structure, which starts as a (b) (4) hydrogel and transitions to a more (b) (4) layer in the mature tissue.

In order to track synthesis and accumulation of human extracellular matrix (ECM), studies used (b) (4) at different times during manufacture.

(b) (4) *studies show:*

STRATAGRAFT actively synthesized (b) (4) (predominant structural components). Synthesis of (b) (4) collagen was further confirmed by (b) (4), a specific metabolite associated with biosynthetic processing of type I collagen **(Table 29)**.

(b) (4) collagens are deposited and organized during manufacture including accumulation of (b) (4) of which function *in vivo* to guide assembly of collagen structures. STRATAGRAFT was demonstrated to (b) (4)

Absence of these ECM molecules in freshly poured DE indicates that the cellular components of STRATAGRAFT transform the nascent DE during the STRATAGRAFT maturation process to include human ECM components with central roles in the structural and signaling functions of skin tissue.

(b) (4) **Study for estimates of** (b) (4) **Collagen Synthesis.**

(b) (4)

(b) (4)

The data support that a minimum of approximately (b) (4) of (b) (4) collagen is synthesized and incorporated as mature protein into the mature DE of the drug product.

QUANTIFICATION OF TOTAL COLLAGEN

The (b) (4) data discussed above demonstrated *in vitro* biosynthesis of (b) (4) collagen during manufacturing and provided an estimated amount of (b) (4) collagen to be at least (b) (4) per tissue.

Additional studies were performed to quantify the total collagen content in STRATAGRAFT tissue. Both rat and human type I collagen are comprised of 12 – 14% hydroxyproline by mass. A (b) (4) assay kit for measurement of total hydroxyproline was used to quantify total collagen in the STRATAGRAFT. Residual rat tail tendon collagen was then estimated (b) (4) from total measured collagen. Then the estimated (b) (4) collagen was (b) (4) in the final product to approximate the relative contribution of rat tail tendon type I collagen and (b) (4) in STRATAGRAFT.

(b) (4) cryopreserved tissues from each of (b) (4) lots of STRATAGRAFT were evaluated for total collagen content as shown in Table 30.

Table 30. Collagen Content in STRATAGRAFT

(b) (4)

(b) (4)

(b) (4)

CONTRIBUTION OF COLLAGEN COMPONENT TO STRATAGRAFT MECHANICAL PROPERTIES

The exogenous rat tail collagen gel provides an initial physiological substrate for the input NHDF and NIKS cells but does not contribute substantially to the final mechanical properties of the tissues. Mechanical properties of tissues (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Review Comment: The applicant presented several types of evidence and literature to address the role of rat tail collagen during manufacture and in the final product.

1. (b) (4) data showed that extensive remodeling of the extracellular matrix occurred when human cells are mixed with rat tail collagen
   (b) (4)
2. The tissue condensed and remodeled extensively during manufacture. (b) (4) testing showed that the contributions to the (b) (4) of the final product from rat tail collagen were much less that the contributions from the human cells which formed the stratified dermal and epidermal layers
3. Literature cited by the sponsor support the idea that collagen signaling stimulates the human cells to remodel and differentiate into the skin-like final product

Based on immunhistological analysis of collagens and other ECM proteins, analysis of collagen biosynthesis during manufacture, and biochemical analysis of collagen present in the final product, there is substantial evidence supporting the conclusions that the rat collagen primarily serves to stimulate differentiation and extracellular matrix remodeling during the initial stages of manufacture and that secretion of human collagen and other ECM components by the human cells plays a primary important role in providing the biological functions, structural integrity, and mechanism of action of the final product.

3.2.P.2.3 Manufacturing Process Development

The final STRATAGRAFT drug product is manufactured continuously from the drug substance, (b) (4) prior to cryopreservation. A description of the drug substance manufacturing process is provided in Section 3.2.S.2.2 Description of Manufacturing Process and Process Controls. Significant changes to the manufacturing process and equipment and comparability studies spanning the (b) (4) different stages of process development are described above in 3.2.S.2.6 Manufacturing Process Development. The clinical use of product manufactured at each stage of development is also summarized in this section.

The drug product manufacturing process consists of cryoprotectant treatment, packaging, and cryopreservation of the DP.

Cryopreservation Process Development History

DP cryopreservation process evolved from early studies with (b) (4) to cryopreservation of the final product at -80^{0}C as summarized below. Table 31 presents the major development and the manufacturing sites where the changes took place.

Table 31. StrataGraft Production Methods – Major Process Changes

(b) (4)

The final DP is manufactured (b) (4) transfer of the Tissue Insert and DS into product packaging, and storage of the packaged product at -80 ± 10ºC.

The following parameters were systematically evaluated during development of the cryopreservation process:

- Composition of cryopreservation solution
- Number of cryopreservation solutions required
- Glycerol concentration of the cryopreservation solution
- (b) (4) cryoprotectant treatment temperature(s)
- (b) (4) cryoprotectant treatment time(s)
- Rate and temperature of freezing
- Storage temperature
- Final product packaging
- Shipping conditions
- Thaw temperature and time
- Conditions for post-thaw hold including:
    - Post-thaw hold chamber configuration
    - Post-thaw Hold Solution
    - Post-thaw hold temperature
    - Post-thaw hold time

The cryopreserved DP is supplied with Hold Solution and a Hold Dish. The Hold Solution is used to prepare the thawed tissue in a clinical setting. The Hold Solution is used to rinse and hydrate the tissue prior to meshing and application to the burn site.

A sterile Hold Dish, which is identical to the Product Dish, is provided for clinical convenience to provide a sterile surface to rinse and hold the skin tissue in the clinical setting.

Cryopreservation Solution Composition

The Applicant chose glycerol as cryoprotectant for STRATAGRAFT tissue based on its widespread use in the cryopreservation of human cells and tissues, its safety profile, and low toxicity. Glycerol has been classified by the FDA as generally recognized as safe (GRAS) when used under good manufacturing practices (21 CFR 182.1320) and is a major component of pharmaceutical preparations, burn and wound creams, and other topical skin care products.

Review note: PT review found that these conditions for glycerol use were acceptable.

The glycerol used in the Applicant's cryopreservation solution is (b) (4) material that undergoes (b) (4) prior to release. In addition to glycerol, the cryopreservation solution contains (b) (4)

Long-term cryopreservation process development began with Process (b) (4) and tested elaborate procedures with (b) (4) Variations on packaging configurations were also included.

Subsequently Storage in (b) (4) is not possible for many hospitals and burn centers. The Applicant tested cold storage conditions and using equipment commonly found in hospitals and burn centers. (b) (4) was compared to storage in a -80 °C freezer or in a (b) (4) °C freezer. Tissue architecture and other lot acceptance criteria were acceptable when STRATAGRAFT was stored at (b) (4) °C or lower for at least (b) (4).

The next study compared longer-term storage at (b) (4) °C and (b) (4) °C for 1, 3 or 6 months. This study showed that storage at -80°C, but not at (b) (4), maintains key tissue properties for up to 6 months and allows for longer-term storage at a temperature which is readily available in most burn centers and hospitals.

The next studies were conducted to simplify by (b) (4) determining an optimal glycerol concentration. These studies showed that tissues maintained acceptable quality when treated in a (b) (4) cryopreservation process at (b) (4) in media containing as low as (b) (4) glycerol prior to transfer to -80°C.

The next studies compared quality attributes of STRATAGRAFT frozen using a (b) (4) freezer compared to those frozen by (b) (4) to -80°C. Tissues undergoing (b) (4) to -80^{0}C were all of acceptable quality.

The Applicant next studied ways to streamline the thaw procedure for cryopreserved STRATAGRAFT since this would be done in operating rooms by clinical staff. In order to develop a simple and robust thaw procedure which required minimal training. Tissues were thawed (b) (4) Both conditions resulted in product with acceptable and equivalent viability and tissue structure and met all tested lot-release criteria.

The Applicant next did studies to simplify and streamline the thaw process by testing the feasibility of removing the (b) (4) insert containing STRATAGRAFT after incubation with cryopreservation solution and transferring it to an empty 100 mm tissue culture dish for final packaging. Results showed that STRATAGRAFT stored in the absence of excess cryopreservation solution maintain robust viability.

Thaw and post-thaw hold temperature and time

The Applicant studies showed that tissues thawed for up to 10 minutes at temperatures ranging from (b) (4) exhibit similar post-thaw properties. These are well within the range of temperatures commonly used for burn surgeries. Subsequent process development studies simplified and ensured flexibility regarding post-thaw hold times to provide flexibility for unpredictable operating room timing.
Studies demonstrated that the STRATAGRAFT held at these temperatures for as little as 15 minutes or as long as 4 hours retain key biological tissue properties. These data supported the use of a post-thaw hold chamber from 15 minutes to up to 4 hours to achieve the desired operating room flexibility.

Comparability Studies
As described in 3.2.P. 3.3.2.6. comparability study was designed to evaluate key physical and biological properties of STRATAGRAFT that was cryopreserved at -80^{0}C compared to tissue that was stored (b) (4) . The study showed the tissue constructs were comparable in viability, barrier function, histology, appearance, and sterility. This supported implementation of cryopreservation of STRATAGRAFT made in Process (b) (4) and used for the 3rd patient cohort of the STRATA2011 clinical study.

Development of the Intended Commercial Cryopreservation of STRATAGRAFT–Process (b) (4)
Further development of cryopreservation process examined possible refinement by evaluating the following parameters:

- Glycerol concentration of the cryopreservation solution
- (b) (4) cryoprotectant treatment temperatures
- (b) (4) cryoprotectant treatment times
- Adoption of a (b) (4) Product Dish for cryopreservation
- Execution of the thaw and post-thaw hold step within the Product Dish

Results of the comparability study, provided in section 6.1.4 of 3.2.S.2.6 Manufacturing Process Development showed that rectangular, 100 cm^2 STRATAGRAFT manufactured and cryopreserved after treatment at (b) (4) with cryopreservation solution containing (b) (4) glycerol exhibit key biological and physical properties that:

1. Meet all tested lot-release criteria established for STRATAGRAFT
2. Are comparable to those of circular, (b) (4) cm^2 STRATAGRAFT tissues cryopreserved after treatment at (b) (4)
3. Fall within the ranges of values from QC lot release testing of (b) (4) STRATAGRAFT tissue lots produced for clinical use during the STRATA2001 and STRATA2011 clinical trials.

The results of this comparability study supported implementation of the simplified processes and the rectangular tissue geometry and size for STRATAGRAFT manufacturing.

Development of the Commercial Cryopreservation of STRATAGRAFT –Process (b) (4)
Process (b) (4) was implemented to facilitate scale out of the number of tissues per lot. (b) (4) the batch size was accomplished by processing (b) (4) numbers of tissues within the (b) (4)

(b) (4) under (b) (4) environmental conditions utilizing (b) (4) materials and procedures. The changes introduced to cryopreservation of STRATAGRAFT incorporated the following changes:

(b) (4)

Commercial Packaging Configuration

Manufacturing process (b) (4) for rectangular, 100 cm^2 STRATAGRAFT concluded with packaging and storage of the final tissue product in (b) (4) that was used to manufacture the tissue. Each (b) (4) was heat sealed inside a (b) (4) laminated foil pouch.

As described in 3.2.P.2-3.4.2, The Applicant developed a smaller, custom Product Dish to 1) reduce storage and shipping requirements, 2) enhance sterility assurance of the final packaged product, and 3) facilitate tissue preparation prior to clinical use. (b) (4) , developed a Product Dish to house the 100 cm^2, rectangular insert that holds STRATAGRAFT. This Product Dish is thermoformed from (b) (4) , which is a medical-grade material composed of (b) (4) that is co-extruded with a proprietary, non-silicone anti-nesting agent. Schematics of this Product Dish are shown in Section 3.2.P.7.1.

Figure 11 shows the final STRATAGRAFT packaging process. STRATAGRAFT is treated with cryopreservation solution at the in the growth chamber. The tissue inserts containing the treated STRATAGRAFT constructs are then transferred to Product Dish in an (b) (4) environment. The Product Dish, tissue insert and construct are then (b) (4) laminated foil pouches. The (b) (4) pouches have peel-open seals that will facilitate opening and aseptic handling of the pouch contents prior to clinical use. Specifications and schematics of the (b) (4) pouches are included in Section 3.2.P.7.1. Pouch closure integrity was evaluated via (b) (4) testing according to (b) (4) as provided in section 3.2.P.2.5 Microbiological Attributes. STRATAGRAFT and final product packaging is shown in **Figure 12.** Together, the Product Dish and (b) (4) pouches provide physical and environmental protection for final product during storage at ultracold temperatures and shipment to clinical sites.

Figure 11. STRATAGRAFT Packaging Process

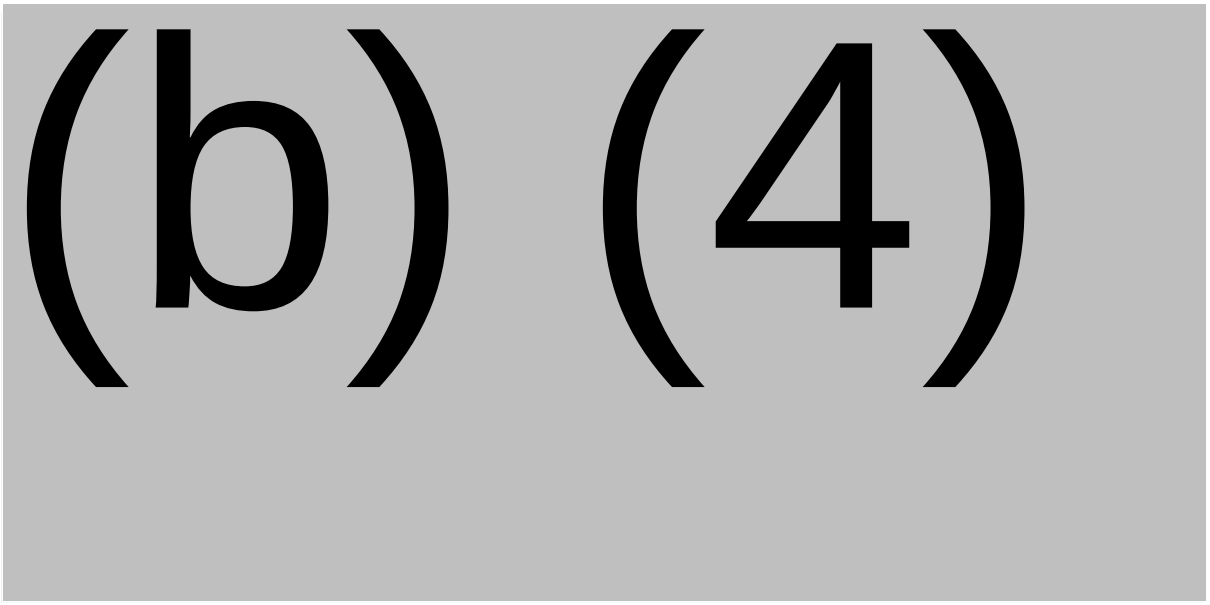
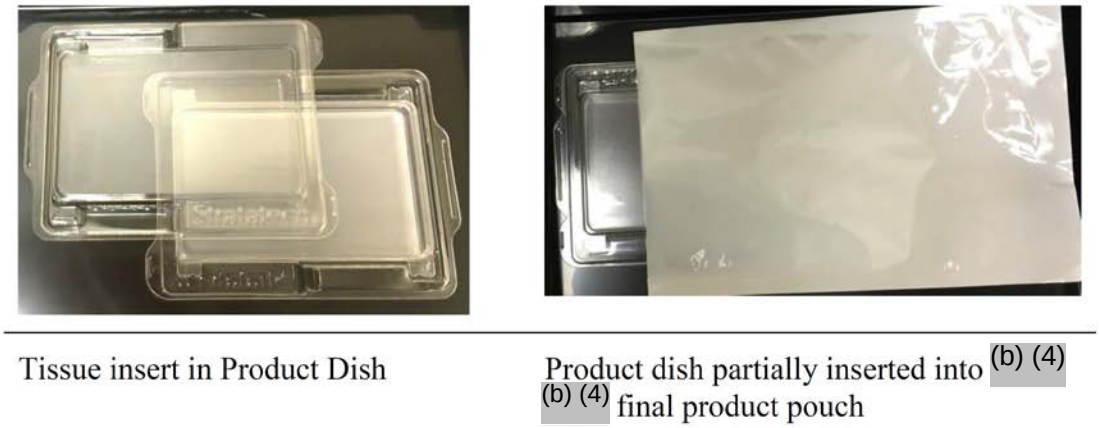


Figure 12. Final Product Packaging



Tissue insert in Product Dish

Product dish partially inserted into (b) (4) (b) (4) final product pouch

Evaluation of Tissues Cryopreserved in 100 cm^2 Product Dishes Using Varied Post-Thaw Hold Conditions

This study was performed to evaluate the performance of the 100 cm^2 Product Dish produced by (b) (4) showed demonstrated that the change to the Product Dish has no effects on the quality attributes of cryopreserved STRATAGRAFT: tissue appearance, histology, barrier function and (b) (4) .

As described in 3.2.P.2.3.5, the final process development studies examined the parameters of STRATAGRAFT thaw and hold steps that would be recommended for product handling at clinical sites. Studies were done to evaluate the robustness of the thaw and hold procedures used to prepare STRATAGRAFT constructs for application during the phase III trial. A FMEA was performed on those procedures and used to identify process steps or parameters which posed the greatest potential risk to impact tissue properties, and studies were designed to evaluate the robustness and determine whether any modifications to clinical instructions or additional control measures should be implemented to help mitigate that risk.

10 Minute Tissue Thaw prior to Preparation for Medical Use

Prior to use, cryopreserved constructs are removed from ultracold temperatures and allowed to warm for up to 10 minutes. This provides time for the cryoprotectant to thaw while the final product packaging is removed. Extended thaws exceeding the 10-minute limit have the potential to negatively impact tissue properties.

A study was performed to both confirm the appropriate performance of the thaw process (<10 minutes), as well as to evaluate the potential impact on tissue properties of deviations. Three lots manufactured with the final process were used. Thaw times included 3,5,10, (b) (4) minutes and ambient temperatures included (b) (4) and 35^{0}C. These represented short, maximum recommended, and beyond maximum thaw durations at room temperature and higher temperature. After these thaw conditions, constructs were transferred to new rectangular growth chambers containing (b) (4) and then analyzed for viability and (b) (4) .

No significant effect of the thaw duration was seen across the times evaluated (p=0.114), but there was a trend toward reduced viability in the Long Duration at RT group.

For (b) (4) analysis showed no significant effect of the ambient temperature during the thaw and hold steps (p=0.108). A significant difference was identified between the control (10 minute) and longest ((b) (4)) thaw duration, these tissues experienced a (b) (4) decrease in (b) (4) . However, variability across the various experimental conditions was lower than that seen between the individual tissue lots, and importantly, all tissues still displayed values meeting the acceptance criteria for lot release, Overall, results were similar between the control and remaining experimental group and fell within the typical ranges for STRATAGRAFT.

Hold Solution Temperature for Tissue Thaw

At the clinical site Hold Solution is used to facilitate the diffusion of cryopreservation solution out of the tissue. A study was performed to evaluate risks around maintaining the target temperature for the hold solution. Based on the Applicant's process development experience, ideal conditions would maintain the tissue and hold solution at 35-39°C during the hold period. Subsequent to the warming step, 15 mL of hold solution is poured into an empty 100 cm^2 Hold Dish for each tissue to be thawed, and the tissues contained within their inserts are transferred to the new dish and placed on top of the Hold Solution. The clinical instructions to the user are to store the hold solution at 2-8°C and warm for a minimum of 15 minutes in a water bath or 45 minutes in a warming oven before application to the tissue This has been identified as an important step in sustaining key biological properties of the tissue.

The study included hold solution temperatures at (b) (4),35, (b) (4) ^{0}C and ambient temperatures of (b) (4) or 35^{0}C. Following the post-thaw hold, constructs were transferred to new growth chambers containing (b) (4) , then analyzed for viability, (b) (4) , and residual glycerol concentration. The results of the tissues exposed to hold solution warmed to temperatures outside the recommended range were compared to the control tissues and to the clinical specification.

Statistical analysis of tissue properties was performed to determine the effects of each parameter.

<u>Viability</u>

All viability values met the lot release criteria at (b) (4) post-thaw ((b) (4)). However, there was a significant effect of both the hold solution temperature (p<0.001) and the CPS treatment time during manufacturing (p<0.01) on the resulting tissue viability. There was no significant effect of the ambient room temperature (p=0.622).

(b) (4)

(b) (4)

Glycerol Content of STRATAGRAFT

A study examined remaining glycerol content in STRATAGRAFT following a thaw. Hold Solution at 35 to 39°C was added to a new Hold Dish. The insert containing the construct was placed in the Hold Dish and the tissues were held at ambient temperature for 15 minutes to 4 hours. The Hold Solution was evaluated for residual CPS by (b) (4) . The constructs (b) (4)

(b) (4) of glycerol is removed from the tissue during the hold for both the short and long hold durations, and residual glycerol concentrations in the tissues in both groups remaining slightly elevated compared to the hold solution. Total residual glycerol in the tissue averaged (b) (4). There is (b) (4) glycerol present in the tissue before the hold step.

Tissue Hold Duration

The clinical instructions specify that tissues should be transferred to the hold dish and kept in the Hold Solution for at least 15 minutes and up to 4 hours. It is not anticipated that standard surgical practices would lead to holds near the 4 hour upper limit, so longer durations were not considered a significant risk.

The effects of Hold Solution duration on STRATAGRAFT properties included groups with short hold times ((b) (4)), and at the recommended times between 15 minutes and 4 hours. Other parameters represent the worst case scenario (within the prescribed ranges) for each hold condition, including thaw durations close to the maximum allowed limit (10 minutes) and ambient temperatures near the low end of the expected operating room temperatures.

Following the post-thaw hold, all tissues (b) (4) and then analyzed with the STRATAGRAFT stability indicating assays of viability (b) (4) .

The results showed relatively consistent performance over the recommended 15 min to 4 hour window. The average tissue viability was well above the lot release specification in all tested groups. There was one viability sample from a construct in the 4 hour/37ºC condition that fell below the lot release specification. However, that other samples from that tissue had very high viability and other tissues from that group did not show similar effects. (b) (4) from tissues in any of the tested groups, although one tissue in the shortest, 5 minute, hold condition fell just below the lot release specification.

Review Comment: These data support the acceptability of the current 15 min to 4 hour time window for the post-thaw hold step at room temperature.

3.2.P.2.4 Container Closure System (LR)

Hold Solution container

The Hold Solution is filled into 20 mL PETG bottles and enclosed with a HDPE screw cap containing a HDPE/LDPE liner. Once the Hold Solution bottles are neck-wrapped and labeled, the Hold Solution is pouched in a (b) (4) pouch consisting of nylon and aluminum foil laminate with an ethylene vinyl acetate copolymer seal. A summary of the primary packaging components of the Hold Solution is shown below.

Table 32. Primary packaging components of the Hold Solution

Component	Description
Bottle	Injection blow molded 20 mL PETG bottle (clear)
Cap	High density polyethylene (HDPE) 20mm closure (white)
	Tri-Seal Liner: Low density polyethylene (LDPE) core sandwiched between two solid layers of high density polyethylene (HDPE)
Label	4 mil white mono-oriented polyolefin film with (b) (4) acrylic adhesive
Neck Wrap	Vinyl Neck Wrap
Pouch	(b) (4) 60ga Nylon, 18 LDPE, 30ga aluminum foil, 14.4 LDPE, 1.5 mil LDPE-EVA

The suitability of the container closure for the Hold Solution was evaluated as follows:

- (b) (4) study: The Hold Solution is kept refrigerated within the foil pouch until preparation for clinical use. The foil pouch includes a 30 gauge layer of aluminum foil, thus (b) (4) is not considered a risk for the Hold Solution.
- (b) (4) : In order to assess the (b) (4) of the Hold Solution packaging, testing was performed on the foil pouch used to package the Hold Solution in accordance (b) (4) Testing results demonstrated that (b) (4) was (b) (4) . Additional testing was done in accordance with (b) (4) to assess the (b) (4) of the pouch. Results demonstrated (b) (4) . The results support that the pouch can provide an adequate barrier from (b) (4) for the Hold Solution.

Reviewer comment: These are not FDA recognized consensus standards. The Applicant was asked to provide the test reports for these studies in Information Request #9 sent on August 18, 2020 and they provided their responses on September 2, 2020 in Amendment 9. The Applicant stated that the (b) (4) testing was conducted by the vendor and provided the test certificates in an appended Section 3.2.P.2.4 – Hold Solution. (b) (4) replicates were evaluated for each test. This information is acceptable.

- Container closure integrity for the primary packaging and foil pouch: Validated as per the studies described in section 3.2.P.2.5 Microbiological Attributes. Additionally, the seal integrity is demonstrated through sterility testing at the time of release and as part of the stability program.

Reviewer comment: Dr. Hector Carrero (CBER/OCBQ/DMPQ) reviewed this information.

- Biological reactivity: In accordance with (b) (4) , the Biological Reactivity tests were conducted on the (b) (4) packaging components according to (b) (4) . Both the bottle and cap were found to be non-cytotoxic.

Reviewer comment: (b) (4) is an FDA recognized consensus standard.

- Extractables and Leachables: The chemical analyses reports provided for the Hold Solution container are summarized in Table 33..

Table 33. Chemical analysis reports for the Hold Solution container

Report #	Test Article	Title	Location in the submission	Date
RPT-STDY-0361	Extractable Evaluation: Hold Solution Packaging	Extractable Study Report of the Container Closure System for Hold Solution	3.2.R.7 Page 304	4/23/2020
RPT-STDY-0360	Leachable Evaluation: Hold Solution Packaging	Leachable Stability Study Report of the Container Closure System for Hold Solution	3.2.R.7 Page 395	4/24/2020

Reviewer comment: Dr. Berk Oktem (CDRH/OSEL) reviewed this information and found the test methods acceptable. No impurities of concern were detected or identified.

STRATAGRAFT container

The Applicant has a single packaging configuration available for commercial use for the 100 cm^2 construct consisting of the following components:

- A tissue insert consisting of a polycarbonate membrane, with (b) (4) micron pores to allow for media exchange, in a polystyrene frame,
- A product dish consisting of a (b) (4) rectangular tray which holds the tissue insert with STRATAGRAFT,
- A laminated foil pouch consisting of polyethylene, aluminum foil, and low density polyethylene.

The materials of contact with the drug product consist of the tissue insert only. However, the construct may indirectly contact the product dish during cryopreservation and clinical use by way of the cryopreservation medium during storage, and Hold Solution during clinical use, acting as a bridge between the tissue insert membrane and product dish. The STRATAGRAFT components are to be kept in the foil pouch until preparation for clinical use. The foil pouch does not contact the drug product during packaging, shipping, or clinical use.

The suitability of the container closure for the tissue was evaluated as follows:

- (b) (4) study: The packaging components which come into contact with STRATAGRAFT are to be kept in cryopreserved conditions within the pouch and cardboard carton until preparation for clinical use. The construct is packaged within the foil pouch until preparation for clinical use. The foil pouch includes a 30 gauge layer of aluminum foil, thus (b) (4) is not considered a risk for STRATAGRAFT. Additionally, the pouched units are to be stored in an 18pt cardboard carton has an (b) (4) . The duration of product (b) (4) is expected to be minimal due to storage of the construct in a -70 to -90°C freezer until preparation for clinical use. Thus, (b) (4) is not considered a risk for STRATAGRAFT.
- Container permeation: (b) (4) permeability studies were conducted on the drug product packaging in accordance with (b) (4) guidance. In order to assess the (b) (4) of the construct packaging, testing was performed by the vendor on the foil pouch material used to package the construct in accordance with (b) (4) . Testing results demonstrated that (b) (4) was (b) (4) . Additional

testing was done in accordance with (b) (4) to assess the (b) (4) of the pouch. Results demonstrated (b) (4) of (b) (4). The results support that the construct pouch can provide an adequate barrier from (b) (4) for the construct.

Reviewer comment: These are not FDA recognized consensus standards. The Applicant was asked to provide the test reports for these studies in Information Request #9 on August 18, 2020 and provided their responses on September 2, 2020 in Amendment 9. The sponsor stated that the (b) (4) testing was conducted by the vendor and provided the test certificates in an appended Section 3.2.P.2.4 – Hold Solution. (b) (4) replicates were evaluated for each test.

- Seal integrity: The primary barrier from microbiological contamination is the pouch, and thus this component was assessed for seal integrity. Container closure integrity was also validated as per the studies described in section 3.2.P.2.5 Microbiological Attributes. Additionally, the seal integrity is demonstrated through sterility testing at the time of release and as part of the stability program.

Reviewer comment: Dr. Hector Carrero (CBER/OCBQ/DMPQ) reviewed this information.

- Biological reactivity: In accordance with (b) (4), the Biological Reactivity tests were conducted according to (b) (4). Either the (b) (4) test was performed on representative (b) (4) components (Tissue Insert and Product Dish). The test articles were considered non-cytotoxic and met the (b) (4) requirements. (b) (4) testing was performed on the Product Dish components and was found to be non-cytotoxic.

Reviewer comment: (b) (4) are FDA recognized consensus standards.

- Extractables and Leachables: The chemical analyses reports provided for the STRATAGRAFT container are summarized in Table 34 below.

Table 34. Chemical analysis reports for the STRATAGRAFT container

Report #	Test Article	Title	Location in the submission	Date
RPT-MISC-2023	Leachate Shipping Study	Suitability of Cold Shipment of Leachate Samples for Extractable and Leachable Studies of the (b) (4) Permeable Support Tray Assembly	3.2.R.7 Page 36	5/12/2020
RPT-STDY-0362	Extractable Evaluation: (b) (4), Tissue Insert	(b) (4) Permeable Support Tray Assembly Extractable Study with (b) (4)	3.2.R.7 Page 90	4/10/2020
RPT-STDY-0363	Leachable Evaluation: (b) (4), Tissue Insert	Leachable Study Report of the (b) (4) Permeable Support Tray Assembly	3.2.R.7 Page 185	4/10/2020
RPT-STDY-0359	Extractable Evaluation: Product Dish and Hold Dish	Extractable Study Report of the Product Dish and Hold Dish	3.2.R.7 Page 482	3/17/2020
RPT-STDY-0358	Leachable Evaluation: Product Dish and Hold Dish	Leachable Stability Study Report for STRATAGRAFT Product Dish and Hold Dish	3.2.R.7 Page 571	3/23/2020

- Reviewer comment: Dr. Berk Oktem (CDRH/OSEL) reviewed this information and found the test methods acceptable. (b) (4) were detected at levels of (b) (4) , respectively. The Applicant was asked to provide a toxicological risk assessment in Information Request #29 to address the risk associated with these elemental impurities. Dr. Abigail Shearin (CBER/OTAT/DCEPT/PTB) reviewed this information and concluded that the information provided in the toxicological risk assessment is acceptable and the levels of (b) (4) in the container closure are well below the permitted daily exposure levels.

3.2.P.2.5 Microbiological Attributes

Reviewer comment: Dr. Hector Carrero (CBER/OCBQ/DMPQ) reviewed this information for the Hold Solution and STRATAGRAFT container closures.
DBSQC reviewers Simleen Kaur and Most Pravid reviewed this information for STRATAGRAFT. Please refer to section 3.2.P.5 for reviews.

3.2.P.2.6 Compatibility

The studies demonstrating the compatibility of cryopreserved STRATAGRAFT with the Hold Solution are provided in section 3.2.P.2.3.5 Preparation of STRATAGRAFT Tissue for Testing and Clinical Use. For late-stage clinical studies, STRATAGRAFT was removed from ultracold storage and thawed at ambient temperature for up to 10 minutes. The tissue insert containing the thawed STRATAGRAFT was then aseptically transferred into the sterile field and placed in a new, individually wrapped, sterile Product Dish (designated as the Hold Dish) to which the Hold Solution was added prior to the tissue transfer. Once placed in the Hold Dish, STRATAGRAFT was held for 15 minutes to four hours prior to meshing for clinical application. Similar thaw and post-thaw hold procedures are utilized for lot-release testing of STRATAGRAFT tissue and were also used in the comparability studies (outlined in Section 6.1.5 of 3.2.S.2.6) and studies described below. A series of studies were performed to evaluate the robustness of the procedures used during the phase III trial to thaw and prepare STRATAGRAFT for application to wounds. A Failure Mode and Effects Analysis (FMEA) was performed on those procedures and used to identify process steps or parameters which posed the greatest potential risk to impact STRATAGRAFT properties, and studies were designed to evaluate the robustness and determine whether any modifications to clinical instructions or additional control measures should be implemented to help mitigate that risk.

- 10 Minute Tissue Thaw Duration: A study was performed to both confirm the appropriate performance of the process over the currently defined time range, as well as to evaluate the potential impact on STRATAGRAFT properties of deviations to the prescribed procedures. Three lots were evaluated in the study, with thaw durations being 3, 10, (b) (4) minutes at either (b) (4) or 35°C. Viability (b) (4) were evaluated. There was a slight decrease in viability for longer thaw durations, but there were no significant differences between the control and any group. The same trend occurred for (b) (4) .
- Hold Solution Temperature for Tissue Thaw: Based on the Applicant's process development experience, ideal conditions would maintain STRATAGRAFT and the hold solution at 35-39°C during the hold period. Subsequent to the warming step, 15 mL of hold solution is poured into an empty 100 cm^2 Hold Dish for each STRATAGRAFT construct to be thawed, and products contained within their inserts are transferred to the new dish and placed on top of the Hold Solution. This has been identified as an important step in sustaining key biological properties of STRATAGRAFT. An (b) (4) datalogger thermometer was used to record the temperature of the Hold Solution during the warming and cooling processes. The results show that the minimum requirements communicated to the user to store the Hold Solution at 2-8°C and warm for a minimum of 15 minutes in a water bath or 45 minutes in a warming oven before application to STRATAGRAFT are sufficient to warm the Hold Solution. The cooling profile of the Hold Solution was also evaluated and it was demonstrated that the Hold Solution cools significantly faster in the dish than the bottle. These results suggest that instructions should be written to favor delays between the removal of the hold solution bottles from the warmer and subsequent pouring into the dish, in order to minimize possible delays between pouring the hold solution and subsequent STRATAGRAFT transfer.

- Tissue Performance with Various Hold Solution Temperatures: The effects of Hold Solution temperature on the resulting STRATAGRAFT properties was evaluated using 3 lots of STRATAGRAFT. STRATAGRAFT was thawed for 8 to 10 minutes, and 15 mL of STRATAGRAFT Hold solution was added to a new final product dish for each STRATAGRAFT being thawed. After the thaw was complete, STRATAGRAFT constructs contained within their inserts were transferred to the hold dishes and held under the specified conditions. The experimental groups were chosen to explore the STRATAGRAFT response to Hold Solution at temperatures above, below, and within the recommended temperature range (35 to 39°C). All STRATGRAFT constructs were held for 15 to 20 minutes after the addition of Hold Solution. Analysis showed a significant effect of both the hold solution temperature ($p<0.001$) and the Cryopreservation Solution treatment time during manufacturing ($p<0.01$) on the resulting STRATAGRAFT viability, but indicated there was no significant effect of the (b) (4) ($p=0.622$). Post-hoc comparisons showed a significant decrease in the viability of STRATAGRAFT treated with hold solution that was (b) (4) when compared to controls. Analysis showed that there is a significant effect of the hold solution temperature on the resulting STRATAGRAFT (b) (4) ($p<0.05$), but no significant effects of either the (b) (4) ($p=0.578$) or the Cryopreservation Solution treatment time used during manufacturing ($p=0.624$). Similar to what was observed for STRATAGRAFT viability, post-hoc analysis showed that there was a significant decrease in (b) (4) compared to the controls in STRATAGRAFT constructs treated with hold solution that was not warmed prior to use ($p<0.01$).
- Glycerol Content of STRATAGRAFT: STRATAGRAFT constructs were removed from ultracold storage and thawed for no more than 10 minutes at (b) (4). Following the thaw, Hold Solution that had been warmed at 35 to 39°C is added to a new Hold Dish. The insert containing the STRATAGRAFT construct was placed in the Hold Dish and the constructs were held at ambient temperature for 15 minutes to 4 hours. After the hold, all constructs underwent evaluation for tissue mass and volume and a subset of constructs were evaluated for residual Cryopreservation Solution. The study evaluated a total of (b) (constructs where STRATAGRAFT constructs (b) (4) underwent a 4 hour hold and constructs (b) (4) underwent a 15 min hold in Hold Solution. The results showed that (b) (4) of glycerol is removed from STRATAGRAFT during the hold. Results were comparable for both the short and long hold durations, and residual glycerol concentrations in STRATAGRAFT in both groups remained slightly elevated compared to the hold solution. Total residual glycerol in the tissue averaged (b) (4) of the (b) (4) present in the tissue before the hold step.
- Glycerol Content of Residual Hold Solution: Since fluid temperatures could affect transport rates, it is important to evaluate whether changes in the hold conditions could lead to significantly more glycerol being transferred to the patient. At the completion of the post-thaw hold step, the residual hold solution was collected for subsequent testing. There is a general trend of increasing glycerol content in the hold solution with increasing temperatures of both the hold solution and the ambient environment; this reflects greater

removal of glycerol from the tissues under those conditions. In addition to the hold conditions, the amount of glycerol extracted from STRATAGRAFT during the hold also depends on the total Cryopreservation Solution contained in the final product prior to the hold. Analysis of (b) (4) data showed significant effects of hold solution temperature ($p<0.05$), (b) (4) erature ($p<0.05$), and Cryopreservation Solution treatment time used during manufacturing ($p<0.001$) on the amount of glycerol extracted from STRATAGRAFT, with all three parameters positively correlated with greater glycerol levels in the hold solution. Although the post-hoc testing found that the results were comparable between the control and experimental groups (there were no significant differences), there was a trend towards increased glycerol removal in the groups treated with hold solution at temperatures above the current clinical range. Cell viability and (b) (4) were also evaluated for the experimental groups. Only minor differences were observed in any of the tested experimental conditions, and no decreases in STRATAGRAFT properties were observed in any conditions that used solution at the ambient temperature or above. This provides confidence that the critical step is the initial warming of hold solution to a minimum of the (b) (4) – any warming beyond that threshold may provide additional benefit, but is not critical to achieve acceptable STRATAGRAFT properties. The results show that treatment of STRATAGRAFT with Hold Solution that is colder than (b) (4) may be associated with modest decreases in STRATAGRAFT properties, as well as a trend towards less complete removal of glycerol from STRATAGRAFT, and therefore should be avoided. However, it is notable that even use of Hold Solution kept at refrigerated temperatures does not result in catastrophic reductions in STRATAGRAFT properties.

- Tissue Hold Duration: The effects of Hold Solution contact duration on STRATAGRAFT properties were determined utilizing constructs from three independent lots, with each experimental condition using three constructs (one from each lot). Constructs were thawed for 8 to 10 minutes at (b) (4), and then transferred to hold dishes containing the warmed Hold Solution. The experimental groups were chosen to explore the STRATAGRAFT response to hold times below (b) (4) minutes), and at the recommended boundaries of 15 minutes and 4 hours. Other study parameters were selected to represent the worst case scenario (within the prescribed ranges) for each hold condition, including thaw durations close to the maximum allowed limit (10 minutes) and (b) (4) near the low end of the expected operating room temperatures. The results of this study showed excellent robustness of the process against shorter hold durations and confirmed relatively consistent performance over the recommended 15 min to 4 hour window.

The compatibility of the STRATAGRAFT drug product with the container closure system, and leachable and extractable from components of the container closure system, have been studied and discussed in section 3.2.P.2.4 Container Closure System. The container closure integrity study for the drug product is provided in section 3.2.P.2.5 Microbiological Attributes.

The stability of the drug product in the container closure system has been demonstrated and is discussed in section 3.2.P.8.1 Stability Summary and Conclusions.

Overall Reviewer's Assessment of Section 3.2.P.2:

- The information provided is acceptable as submitted or revised in interactive review. Information on product development, components of the drug product and characteristics related to the proposed mechanism of action, and manufacturing development leading to optimal cryopreservation and thaw conditions all support production and use of a quality product. Information on the novel container closure system, novel approaches to assessment of sterility, mycoplasma, and endotoxin assessment are all well described and acceptable. Compatibility of the product with container closure and cryoprotectant are also well described and acceptable. The information is adequate to support approval of this license application.
- State if deficiencies were identified and how they were resolved.
  - The Hold Solution and STRATAGRAFT Product Container were tested for (b) (4) testing but tests did not use FDA-recognized consensus standards. The Applicant was asked to provide the test reports for these studies in Information Request #9 sent on August 18, 2020 and they provided their responses on September 2, 2020 in Amendment 9. The Applicant stated that the (b) (4) testing was conducted by the vendor and provided the test certificates in an appended Section 3.2.P.2.4 – Hold Solution. (b) (4) replicates were evaluated for each test. This information is acceptable.
  - Dr. Berk Oktem (CDRH/OSEL) reviewed information on E&L testing of the STRATGARAFT container and found the test methods acceptable. However, (b) (4) were detected at levels of (b) (4), respectively. The Applicant was asked to provide a toxicological risk assessment in Information Request #29 to address the risk associated with these elemental impurities. Amendment 26 contained this information. Dr. Abigail Shearin (CBER/OTAT/DCEPT/PTB) reviewed this information and concluded that the information provided in the toxicological risk assessment is acceptable and the levels of (b) (4) in the container closure are well below the permitted daily exposure levels
-

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

The facilities involved in the manufacture, testing, packaging, and stability testing, of STRATAGRAFT.

Skin Tissue are provided below. Sites used for clinical manufacture and not used for commercial manufacturing are provided below.

Sites and Responsibilities in Manufacture of StrataGraft

Site/Facility	Responsibility
Stratatech Corporation 535 Science Drive Madison, WI 53719	Drug product manufacturer Analytical testing (appearance, sterility, viability, barrier function, histology, (b) (4), bacterial endotoxin) Primary packaging Secondary packaging Stability testing
(b) (4)	Analytical testing (mycoplasma)
	Container Closure Integrity for Stability testing

Clinical Sites for the Manufacture of STRATAGRAFT

Site/Facility	Responsibility
(b) (4)	Drug product manufacture
Stratatech Corporation 510 Charmany Drive, Suite 150 Madison, WI 53719	Analytical testing (appearance, sterility, viability, barrier function, histology, (b) (4)) Stability testing

3.2.P.3.2 Batch Formula

(SB)
A batch size of (b) (4) tissue construct may be used for the commercial manufacturing process. The dosage form is one tissue construct of 100 cm^2. Multiple doses may be needed to cover large treatment areas

(LR)
The Cryopreservation Solution is an excipient for the final product. The batch formula of the final product consists of (b) (4) of the Cryopreservation Solution per (b) (4) tissue batch size and (b) (4) of Cryopreservation Solution per (b) (4) tissue batch size. The components which comprise the Cryopreservation Solution are provided in Table 2 of Section 3.2.P.3.2 of the submission.

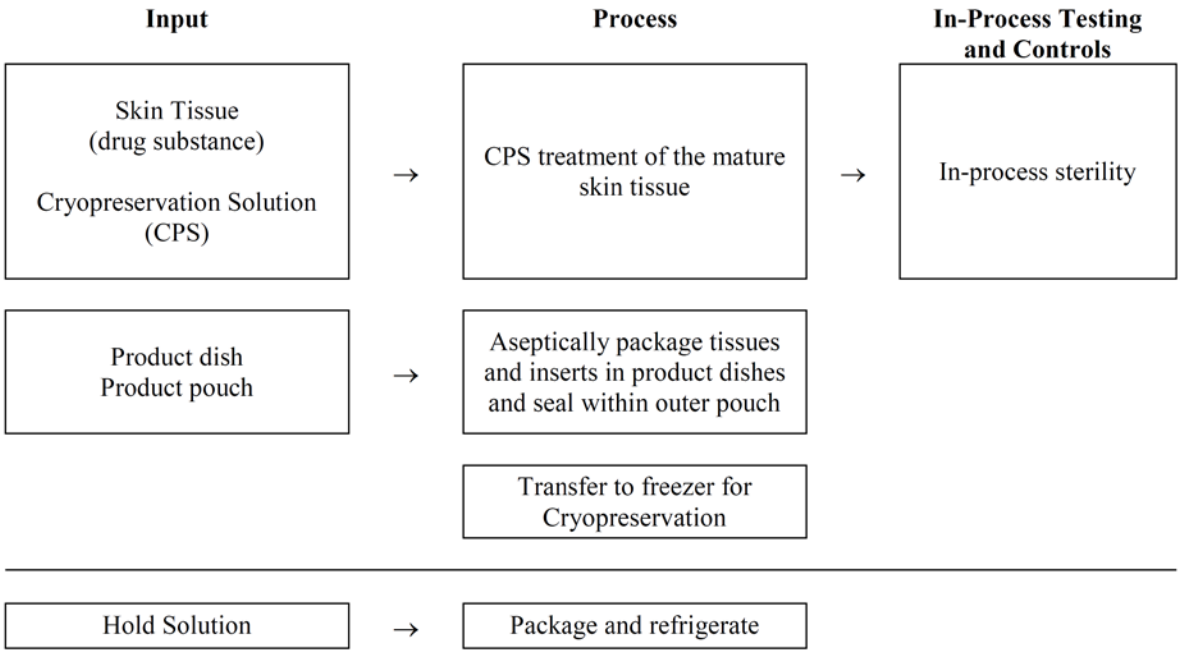
The Hold Solution is an excipient that is provided in a 15 mL/bottle format as a clinical aid to thaw and maintain the biological function of STRATAGRAFT during surgical preparation. The components which comprise the Hold Solution are provided in Table 3 of Section 3.2.P.3.2 of the submission.

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:
- The information provided for these two section is acceptable as submitted.
- No deficiencies were identified and no information requests were sent to the Applicant.
-

3.2.P.3.3 Description of Manufacturing Process

A comprehensive description of STRATAGRAFT construct manufacturing is presented in 3.2.S.2.2 Description of Manufacturing Process and Process Controls.
This is a summary of the entire process entailing construct manufacturing, packaging and cryopreservation as well as hold solution manufacture, packaging, and refrigeration.
Manufacturing Process Flow Diagram
A flow diagram for the manufacturing and packaging processes for STRATAGRAFT is shown below.

Figure 13. Manufacturing Process Flow Diagram



Manufacturing Process Description

This describes the process steps for STRATAGRAFT production at the (b) (4)-tissue lot sizes. The steps are repeated for the (b) (4)-tissue batch size. The cryopreservation and packaging steps begin immediately after completion of manufacturing the STRATAGRAFT construct, after the culture media has been aspirated from each of the growth chambers.

Cryopreservation: (b) (4)

Following the removal of (b) (4), the tissues are (b) (4) The packaged tissues are then stored at (b) (4) to -90°C for a minimum of (b) (4) prior to initiation of lot-release testing and transfer to quarantine storage. The spent CPS solution is collected and submitted to QC for in-process sterility testing.

Hold Solution Labeling and Packaging

Pre-labeled and pre-pouched Hold Solution bottles are packaged in a cardboard box and refrigerated (2° to 8°C).

Critical Process Parameters

Critical Process Parameters (CPP), Key Operating Parameters (KOP), and Non-Key Operating Parameters (NKOP) were evaluated using a risk-based approach for STRATAGRAFT manufacturing. The parameters are based on historical operating limits, results from process characterization and robustness experiments, and trended results compiled from recent STRATAGRAFT manufacturing runs at the final manufacturing facility. A summary of the CPPs are provided below.

Table 35. Summary of CPPs for the STRATAGRAFT Manufacturing Process

Parameter	Target Set Point	Characterized Range	PAR
CPS treatment time	(b) (4)		
Tissue packaging time			

Table 36. Key Operating Parameters for the STRATAGRAFT Manufacturing Process

Parameter	PAR
Tissue Cryopreservation	
Ultra-cold freezer temperature	(b) (4) to -90 °C
Freeze time	(b) (4)

Batch Numbering System
A unique sequential 10 digit number is generated by the Enterprise Resource Planning (ERP) system and assigned to each lot of final product. This number is used throughout the manufacturing process. Additional items assigned numbers in the ERP system include supplies, raw materials, and intermediate product. All materials are assigned numbers from the same sequential bank and each material, regardless of classification, is assigned the next available number at the time of assignment.

Overall Reviewer's Assessment of Section 3.2.P.3.3:
- ❑ The information provided is acceptable as submitted.
- ❑ No deficiencies were identified.
- ❑ List any remaining deficiencies that should be included in a CR letter.

3.2.P.3.4 Controls of Critical Steps and Intermediates

Controls of Critical Steps and Intermediates

Controls of Critical Steps and Intermediates is covered in 3.2.S.2.5. Control of the final steps of manufacturing including cryopreservation and development of thawing procedures are described in 3.2.P.2.3 Manufacturing Process Development

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Overall Reviewer's Assessment of Section 3.2.P.3.4:
- ❑ The information provided is acceptable as submitted.
- ❑ No deficiencies were identified and how they were resolved.
- ❑ No remaining deficiencies that should be included in a CR letter.

3.2.P.3.5 Process Validation and/or Evaluation

All information on process validation in the application is found in this section due to the continuous manufacturing process and the lack of a held intermediate.

The PPQ evaluated key operating parameters and in-process controls for NHDF and NIKS cell expansion and added evaluation of critical process parameters for organotypic culture and cryopreservation of the final product. In addition, environmental monitoring was conducted

The PPQ manufacturing evaluation included (b) (4) lots ((b) (4)-unit scale) of STRATAGRAFT constructs (**Table 37**). Although PPQ (b) (4) lots were initially included, there was an incident that precluded use of lot (b) (4) during the stability phase of PPQ. (b) (4) individual constructs were removed from the studies due to media spillage when a cart with (b) (4) constructs (lot (b) (4)) was bumped at the end of the organotypic phase of manufacture. Therefore, lot (b) (4) was included as part of the PPQ to support stability studies of three PPQ lots as per section 3.2.P.8.2.

All drug product lots met lot release criteria. Although lot (b) (4) was not included in stability, other data from this lot was included in PPQ analysis. Stability testing for up to (b) (4) months is being performed. Although manufacturing of (b) (4)-tissue lots is performed, (b) (4)-tissue manufacturing scale was used because it covers all critical steps used during (b) (4)-tissue scale manufacturing.

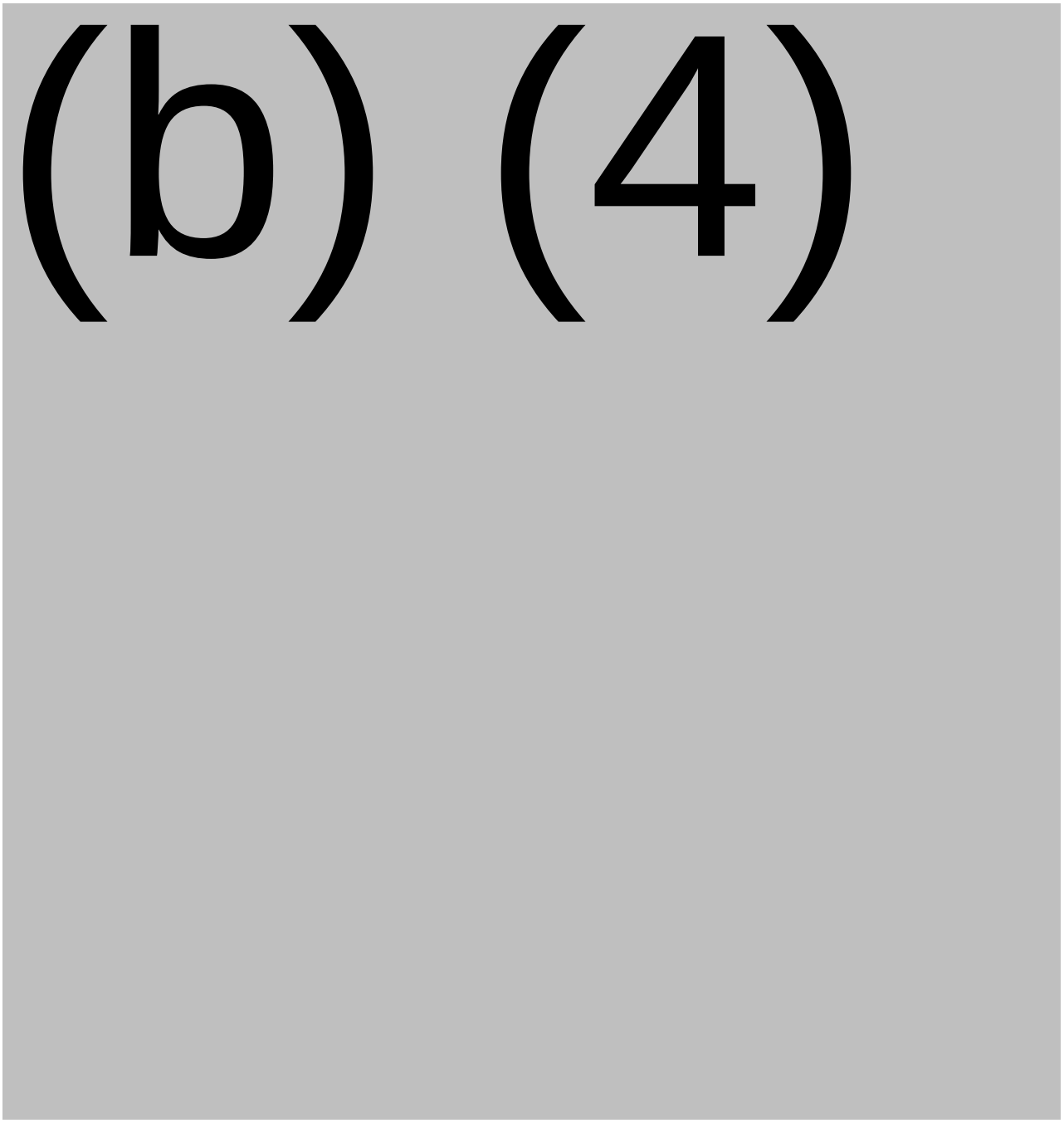
Performance criteria included evaluation of operator and analyst training, materials, facilities, equipment, batch record procedure, and test method verification. Additionally, data obtained during the execution and testing of the validation batches were evaluated against critical process parameters, in-process controls and final lot release criteria.

Table 37. Summary of PPQ Batches

Lot Number	(b) (4)
Lot Size	
Start of Manufacture	
End of Manufacture	

NHDF Monolayer Expansion

A summary of the key operating parameters (KOPs) for NHDF expansion and harvest are provided in **Table 38**. The results of the in-process testing are provided in **Table 39**. All acceptance criteria were met and no microscopic contamination was observed.



NIKS Monolayer Expansion

A summary of KOPs for NIKS expansion and harvest are provided in **Table 40.** The results of the in-process testing are provided in **Table 41**. All acceptance criteria were met and no microscopic contamination was observed.

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

Organotypic Culture

Multiple in-process controls ensure the absence of contamination and appropriate tissue formation in the developing constructs. A summary of the Key Operating Parameters (KOPS) and critical process parameters (CPPs) during manufacture of the PPQ lots are provided in **Table 42** and **Table 43**, respectively.

The results of the in-process testing are provided in **Table 44.** All acceptance criteria were met.

Table 42. Key Operating Parameters for the Organotypic Culture

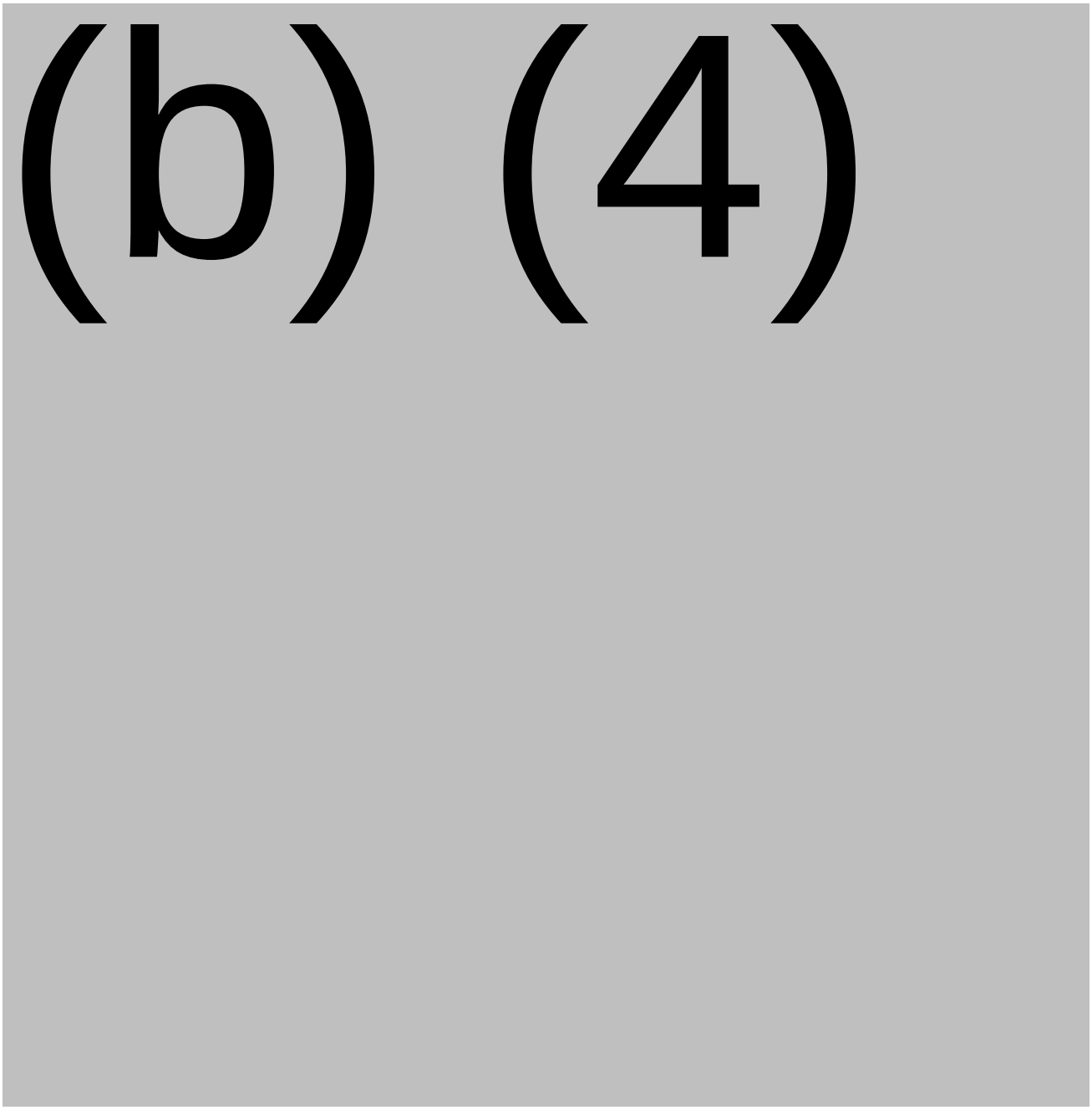
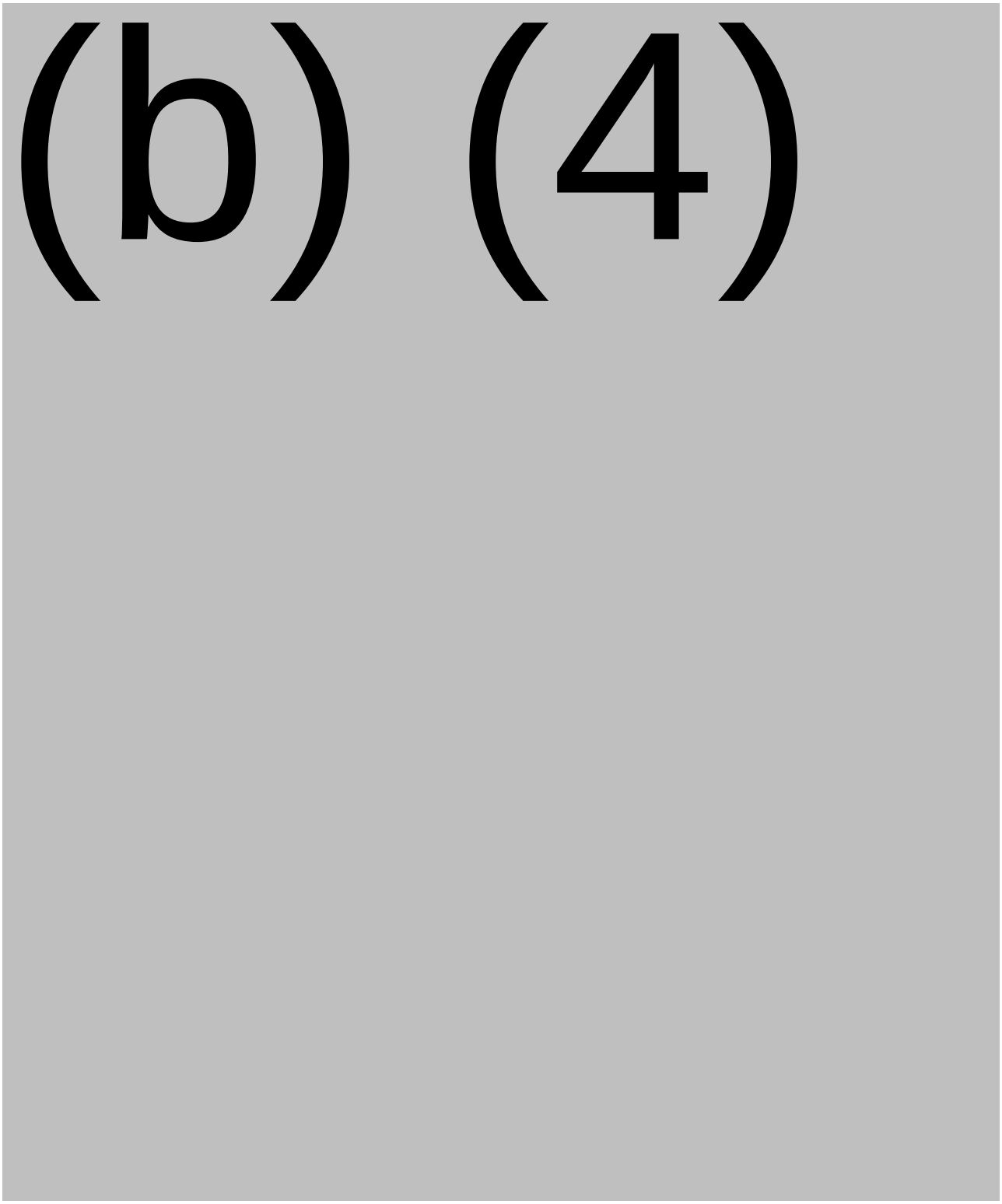


Table 44. In-Process Controls for Organotypic Culture



Cryopreservation
KOPs for tissue cryopreservation included freezer temperatures between (b) (4) to -90 °C and a freeze time of (b) (4) .

CPPs included cryopreservation solution (CPS) treatment times of (b) (4), and subsequent tissue packaging time of (b) (4).
In process controls for cryopreservation included sterility testing of the spent CPS.
All lots met the criteria for the PPQ study.

Drug Product Release Testing

During the time of PPQ studies, the Applicant assessed the (b) (4) PPQ lots in accordance with the clinical specifications under IND 10113. Tissue yields of the (b) (4) lots are presented in **Table 45.** All tissue discards occurred during the organotypic culture phase of manufacture for failure to meet the appearance specification. None of the tissues were discarded due to microbiological contamination. All STRATAGRAFT lots met the release specification acceptance criteria.
The release specifications, as provided in section 3.2.P.5.1, were revised based on cumulative data specification for commercial drug product. Barrier function, sterility, appearance, and histology were the same. The differences were as follows:
- Viability revised (b) (4) from (b) (4)
- (b) (4) was revised (b) (4) from (b) (4)
- Endotoxin was revised (b) (4) from (b) (4)

Mycoplasma was not included in the PPQ studies since the methodology had not been developed.
Stability studies were based on the IND release specifications so had lower specifications for viability, (b) (4), and endotoxin.
Retrospectively, The PPQ lots also meet the proposed commercial specifications.
Reviewer comment: the revised release specifications are acceptable. (b) (4), Endotoxin and mycoplasma specifications for final product were deemed acceptable by DBSQC reviewers MP and SK (see 3.2.P.3.5.2 and .3 below).

Table 45. PPQ Batch Yields

Lot Number	Total Tissues Released
(b) (4)	

Reviewer comments: histology validation was initially unacceptable but was resolved (see Overall Reviewer's Assessment 3.2.P.3.5 and review by TT below in 3.2.P.5.6.2). However, the results of the PPQ are consistent and the clinical effectiveness was established for lots that met this and other lot release criteria used under IND 10113. During PPQ, the endotoxin specification was revised (b) (4) from (b) (4). The revision (b) (4) from (b) (4) would not exceed endotoxin recommendations for parenteral use in the indicated population. Also, topical endotoxin limits are less well established.
The PPQ studies demonstrate that the process is well established and suitable for producing safe and effective product.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

- Overall, the information provided for process evaluation and validation is acceptable and supports the conclusion that a well-controlled manufacturing process is in place and capable of production of product of acceptable quality.
  - As a consequence of PPQ studies, release specifications were revised. Barrier function, sterility, appearance, and histology were the same. The differences were as follows:
    - Viability revised (b) (4) from (b) (4)
    - (b) (4) was revised (b) (4) from (b) (4)
    - Endotoxin was revised (b) (4) from (b) (4)

    Mycoplasma was not included in the PPQ studies since the methodology had not been developed.

    Stability studies were based on the IND release specifications so had lower specifications for viability, (b) (4), and endotoxin. .
- State if deficiencies were identified and how they were resolved.
  - Histology validation was initially unacceptable as submitted but issues were resolved. (see review of TT for 3.2.P.5)
    - After several IRs, communication at the MidCycle meeting, and e-mails, on 12-23-2020 (Sequence 0030), the applicant submitted the histology method Validation Report (RPT-VAL-0105). The revised validation of the histology method for Specificity, Precision and Accuracy, together with the change in the acceptance specification to "(b) (4) " is acceptable.

3.2.P.4 Control of Excipients (LR)

3.2.P.4.1 Specifications (LR)

The Cryopreservation Solution and Hold Solution are excipients. Section 3.2.P.3.2 contains the components of these solutions.

The Cryopreservation Solution is sourced from (b) (4) Certificates of Analysis and Certificates of Origin from the suppliers were provided in Section 3.2.R.1. The quality control specifications for the Cryopreservation Solution are shown in Table 46 below.

Table 46. Cryopreservation Solution quality control specifications

(b) (4)

Reviewer comment: The Applicant stated that identification testing was performed in-house while all other testing results were obtained from the Certificate of Analysis. Additional testing on the Certificates of Analysis which the Applicant does not consider as quality control specifications are (b) (4) testing ((b) (4)) and (b) (4) testing (b) (4)

The Hold Solution is sourced from (b) (4) . A Certificate of Analysis and Certificate of Origin were provided Section 3.2.R.1. The quality control specifications for the Hold Solution are shown in Table 47 below.

Table 47Hold Solution quality control specifications.

(b) (4)

- Reviewer comment: The Applicant stated that identification testing was performed in-house while all other testing results were obtained from the Certificate of Analysis.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

If applicable.

The sponsor provided the (b) (4) methods used to test the identification and quantification of the Cryopreservation Solution and the identification of the Hold Solution. All compendial tests have been verified and follow their respective monographs.

The method for assay and identification of glycerol for the Cryopreservation Solution was validated for precision, method precision, intermediate precision, linearity, accuracy and range, specificity, and stability of standard and sample solutions.

Reviewer comment: The intermediate precision evaluation involved the use of a different operator, instrument, and column (ruggedness).

The method for the identification by (b) (4) for the Hold Solution was validated for precision, method precision, intermediate precision, linearity, accuracy and range, specificity, robustness, and stability of solutions.

Reviewer comment: The intermediate precision evaluation involved the use of a different operator, instrument, and column (ruggedness).

The method for the (b) (4) identification by (b) (4) for the Hold Solution was validated for precision, method precision, intermediate precision, linearity, accuracy and range, specificity, robustness, and stability of solutions

3.2.P.4.4 Justification of Specifications

The vendor of the Cryopreservation Solution is qualified by internal vendor qualification procedures. Upon receipt, the vendor Certificate of Analysis (COA) is reviewed for conformation to the registered specification. The following tests are performed by the vendor and accepted per vendor COA: (b) (4) . Upon receipt of each lot of Cryopreservation Solution, additional identification testing of the material is performed to ensure that the correct component was received and that the component was formulated appropriately. The following identification tests are performed:

(b) (4)

The vendor of the Hold Solution is qualified by internal vendor qualification procedures. Upon receipt of the Hold Solution, the vendor COA is reviewed for conformation to the registered specification. The following tests are performed by the vendor and accepted per vendor COA: (b) (4) . Upon receipt of each lot of Hold Solution, additional sterility and identification testing of the material is performed to ensure that the correct component was received and that the component was formulated appropriately. The following identification tests are performed:

(b) (4)

Identification by (b) (4) – The Hold Solution formulation, as provided in section 3.2.P.3.2 Batch Formula, contains various (b) (4) the formulation of the Hold Solution.

3.2.P.4.5 Excipients of Human or Animal Origin

There are no excipients of human or animal origin used in the manufacture of the Hold Solution or Cryopreservation Solution.

3.2.P.4.6 Novel Excipient

The Cryopreservation Solution contains (b) (4) and glycerol. Glycerol has been classified by FDA as generally recognized as safe (GRAS) when used under good manufacturing practices. The Cryopreservation Solution contains (b) (4) glycerol v/v and the Cryopreservation Solution contains (b) (4) glycerol v/v and approximately (b) (4) of Cryopreservation Solution is typically present in each STRATAGRAFT construct at time of cryopreservation. The majority of the glycerol is removed from the tissue during the post-thaw hold step, with tissues retaining only an estimated (b) (4) of the tissue fluid volume of glycerol at the time of application to the patient. Using a scenario of one treatment with (b) (4) tissues, the maximum daily dose of glycerol from STRATAGRAFT is estimated to be (b) (4) g/day. As part of the health-based risk assessment provided in section 3.2.R – Glycerol Safety Risk Assessment, a Permitted Daily Exposure (PDE) of 60 g/day by the topical dermal route for glycerol is consistent with current risk assessment guidelines in which safety or uncertainty factors are applied to the most sensitive and relevant endpoint of concern. Each of the components of the Cryopreservation Solution are commonly found in cellular growth medium, with the exception of glycerol and (b) (4).

Reviewer comment: Dr. Abigail Shearin, the P/T reviewer for this application, reviewed the Glycerol Safety Risk Assessment.

The Hold Solution is a common, commercially available, cell growth medium consisting of (b) (4). Each of the components of the Hold Solution are commonly found in cellular growth medium, with (b) (4) being the only component in the Hold Solution that is not in the STRATAGRAFT growth medium.

The Applicant states that the safety of the Cryopreservation and Hold Solutions is supported by the overall clinical safety of the drug product, summarized in section 2.7.4 Summary of Clinical Safety. The Applicant also states that STRATAGRAFT has been demonstrated to be safe based upon a total of 119 subjects receiving treatment with cryopreserved STRATAGRAFT, with no unexpected product-related serious adverse events.

Reviewer comment: The information submitted is adequate to support licensure of STRATGRAFT.

Overall Reviewer's Assessment of Section 3.2.P.4:

- ❑ The information provided for control of the excipients, Cryopreservation Solution and Hold Solution is acceptable as submitted.
- ❑

3.2.P.5 Control of Drug Product (TT)
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) (TT)

The release tests and acceptance criteria for the final product are tabulated below:

Table 48. STRATAGRAFT Release Tests

Test	Acceptance Criteria	
	Release	Stability
Appearance	Skin tissue should be translucent and off-white in color, majority of skin tissue surface should be covered by an epidermal layer, minor irregularities wrinkling, contraction, and variation in skin tissue thickness and/or opacity are acceptable	
Histology	(b) (4)	
Viability	(b) (4)	
Barrier Function	(b) (4)	Not Tested
(b) (4)	(b) (4)	
Sterility	No Growth	
Endotoxin	(b) (4)	Not Tested
Mycoplasma	Not detected	Not Tested
Container Closure Integrity (b) (4) [a]	Not Tested	Must be (b) (4)

a Container Closure Integrity testing is performed in lieu of sterility testing (b) (4) (b) (4) as per the post-approval stability protocol.

3.2.P.5.6 Justification of Specifications (TT)

3.2.P.5.6.1 Appearance

The test is a qualitative macroscopic visual assessment of the final product. The acceptance criterion is the observation that the tissue is covered by an epidermal layer and is translucent and off-white in color.

Reviewer Comment: The specification for appearance is justified as it correlates with the barrier function assay and can distinguish immature STRATAGRAFT tissue, that lacks a functional (b) (4), from the final product (process (b) (4)).

3.2.P.5.6.2 Histology

- The test is a (b) (4) visual assessment of the final product. The test is a (b) (4) visual assessment of the final product.
- The acceptance criterion (b) (4)

Reviewer Comment: The initial specification for histological appearance was not acceptable. Based on the data presented in the validation studies, (b) (4) However, the revised specification received on 12-23-2020 (RPT-VAL-0105 Sequence 0030) is acceptable (see below)

3.2.P.5.6.3 Viability

- The viability test quantifies the (b) (4) within the final product by measuring the (b) (4)
- Tolerance intervals were used to establish statistically based ranges for the release specification based on the results from the clinical trials. The calculation of a 95% confidence was utilized to align with the coverage of (b) (4) sigma limits.
- Based on the statistical analysis, the release criterion is set to (b) (4)
    - Note: For stability testing, the acceptance criterion is currently set at (b) (4). This is based on values obtained from development lots and will be reassessed when sufficient information is available to support a statistical analysis of the stability data obtained from commercial lots.

Reviewer Comment: Based on review of the viability validation report, the test and acceptance criteria are acceptable.

3.2.P.5.6.4 Barrier Function

- The barrier function method is a semi-quantitative test that measures (b) (4)

- The specification is based on an average value from development lots, with the lower limit set by subtracting (b) (4) standard deviations.
    - Using this specification, tissues tested at process (b) (4) failed, whereas those tested on process (b) (4) passed. Therefore, the specification is can discriminate between tissues with an (b) (4) .

Reviewer Comment: Based on review of the barrier function assay validation report, the release specification is acceptable.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

- The finalized Drug Product specifications (Appearance, Histology, Barrier Function, (b) (4), Sterility, Endotoxin, Mycoplasma) are acceptable and support production of a quality Drug Product. Changes were introduced to the final specifications subsequent to statistical analysis of data accumulated during PPQ. As a consequence of PPQ studies, release specifications were revised:
  - Viability revised (b) (4) from (b) (4)
  - (b) (4) was revised (b) (4) from (b) (4)
  - Endotoxin was revised (b) (4) from (b) (4)

  Mycoplasma was not included in the PPQ studies since the methodology had not been developed. However, appropriate tests for this type of tissue engineered product were developed, implemented and validated and found acceptable by the DBSQC reviewer (SK: se review 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures).

  The changes of (b) (4) viability and (b) (4) align with the proposed method of action for the Drug Product. These (b) (4) indicate more overall (b) (4) and more production of a biologically active and relevant factor, supporting the potential effectiveness of the DP. The (b) (4) in endotoxin limit does not introduce any safety concerns.
  - Stability studies were based on the IND release specifications so had (b) (4) specifications for viability, (b) (4), and endotoxin.

- State if deficiencies were identified and resolved.
  - Histology validation was initially unacceptable as submitted but issues were resolved.
    - After several IRs, communication at the MidCycle meeting, and e-mails, on 12-23-2020 (Sequence 0030), the applicant submitted the histology method Validation Report (RPT-VAL-0105). The revised validation of the histology method for Specificity, Precision and Accuracy, together with the change in the acceptance specification to (b) (4) is acceptable.
  - A CDRH consult for barrier function assessment resulted in refinement of this specification. The initial specification used values beyond the linear response range of the instrument probe. The specification was revised appropriately (see TT review below [3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures and IR#24 and response in amendment 0021]).
- There are no remaining deficiencies.
- The control strategies include testing and characterization of the NHDF and NIKS WCBs, extensive PPQ studies, appropriate in process testing ((b) (4)) of the phases of manufacturing ((b) (4)), and appropriate final product testing of thawed DP. The final product tests and release criteria are appropriate and align with regulatory requirements for identity, purity, and potency. The release criteria for (b) (4) align support the proposed mechanism of actions relevant to healing of thermal burns. Stability studies (in storage and shipping) are appropriate, and support product expiration dating. The process is well controlled and has demonstrated ability to produce DP of acceptable quality. These conclusions support approval of the BLA.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures (TT, MP, SK)

Table 49 shows test method and validation/verification reports for product release testing.

Table 49. Test Method and Validation/Verification Reports for Product Release

Test	Analytical Method	Validation/Verification Reports
Appearance	SOP-QC-0448	RPT-VAL-0061 (verification report)
Histology	SOP-QC-0452	RPT-VAL-0062 (verification report)
Viability	SOP-QC-0366	VALREP.001 (validation report)
Barrier Function	SOP-QC-0382	VALREP.003 (validation report)
(b) (4)	SOP-QC-0425	VALREP.002 (validation report)
Sterility	SOP-QC-0469	RPT-VAL-0081 (verification report)
Endotoxin	SOP-QC-0505	RPT-VAL-0086 (verification report)
Mycoplasma	M-1400	RPT-VAL-0085 (verification report)

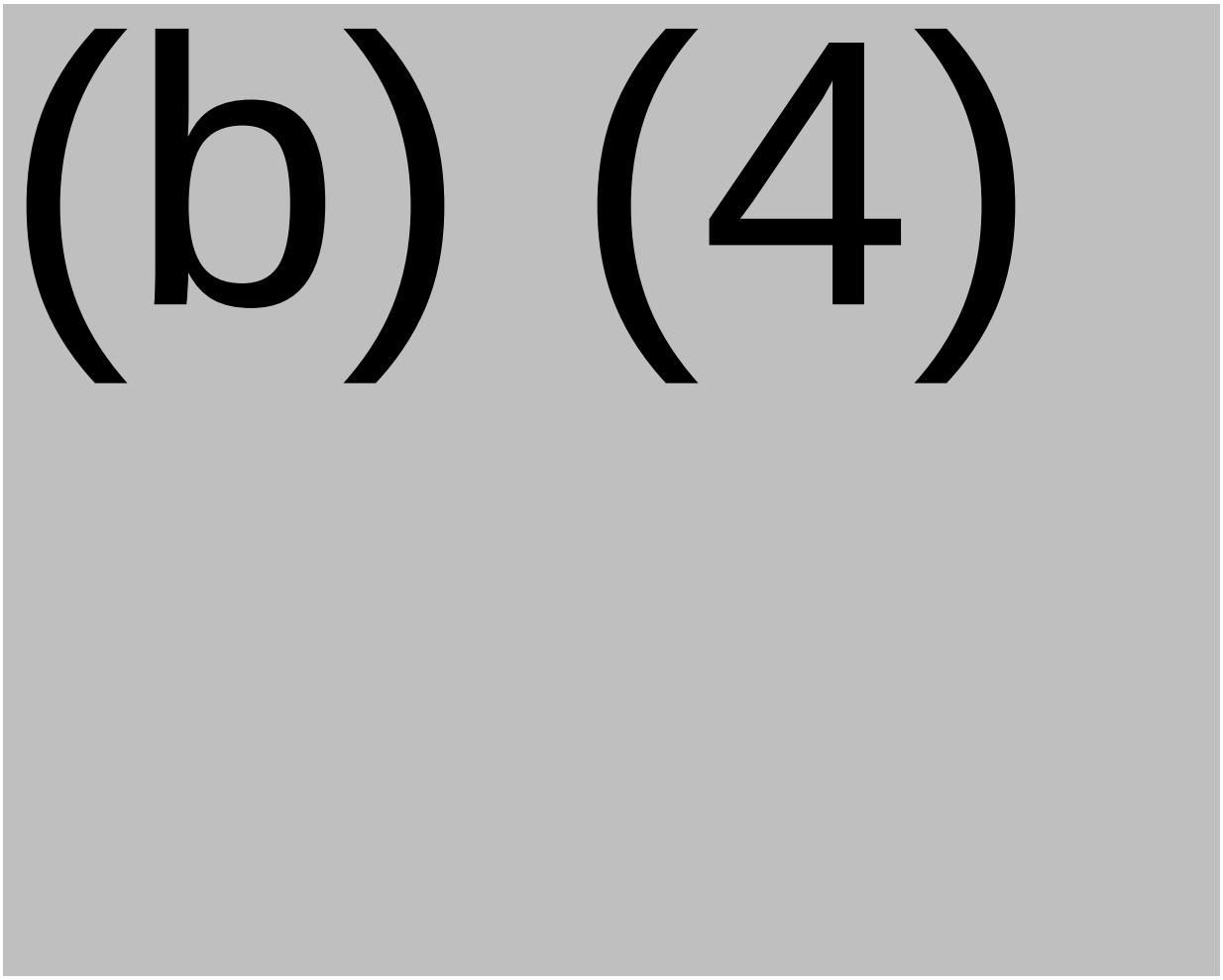
Final Product Sampling Plan

- **The final STRATAGRAFT product is produced in lot sizes of either (b) (4) and release testing is conducted on representative tissues as follows:**
  - (b) (4) of the lot size are tested for sterility.
  - (b) (4) tissues per lot are tested for all other lot-release tests, independent of lot size.

Total number of tissues tested	(b) (4)
Number of tissues tested for sterility	
Number of tissues tested for endotoxin and mycoplasma	
Number of tissues tested for potency (viability, (b) (4) and barrier function)	
Number of tissues tested for identity (appearance and histology)	

- The sampling plan showing the locations of biopsies taken for each release test is shown below:

Figure 14. Sampling Locations for the (b) (4) -Tissue Scale



Reviewer Comment: The sampling plan, as discussed at the pre-BLA meeting, is acceptable.

3.2.P.5.2-1 and 3.2.P.5.3-1 Appearance

Method Summary

- Each STRATAGRAFT final product designated for QC testing is visually inspected for appearance per SOP-QC-0448, in which the tissue is evaluated for:
  - Color, surface coverage, and texture.
    - Mature and differentiated STRATAGRAFT is identified by the majority of the tissue being covered by a translucent and off-white epidermal layer.
    - STRATAGRAFT that appear wet on the epidermal surface lack a mature stratum corneum and are not fully epithelialized.

Summary of Method Validation [Verification report RPT-VAL-0061]:

The appearance method was validated for specificity and intermediate precision to demonstrate consistency between different analysts and their ability to differentiate between the appearance of immature and mature tissues (ADREP.025).

Specificity

- (b) (4) lots of STRATAGRAFT product were assessed (b) (4) after the NIKS seed (process (b) (4)), and on process (b) (4) and the standard cryopreservation time point of process (b) (4).
- Tissues were (b) (4) and analyzed for appearance:
  - Tissues cryopreserved on process (b) (4) failed the appearance test in that they had major irregularities, including (b) (4)
  - Tissues cryopreserved on process (b) (4) met the appearance acceptance criteria defined in the STRATAGRAFT master specification (SPC-FP-0788).

Reviewer Comment: As the appearance test is qualitative, validation for intermediate precision and specificity alone is acceptable. In addition, the appearance test was able to distinguish immature STRATAGRAFT products with a similar accuracy to the barrier function assay.

3.2.P.5.2-2 and 3.2.P.5.3-2 Histology

Method Summary

(b) (4)

Summary of Method Validation [Verification report RPT-VAL-0062]

(b) (4)

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

(b) (4)

3.2.P.5.2-3 and 3.2.P.5.3-3 Viability

Method Summary

- The viability method measures (b) (4)
- (b) (4)

Summary of Method Validation [Validation report VALREP-001]

(b) (4)

Stability-indicating characteristic. Robustness, in terms of the reliability of the method with respect to deliberate variations in the method parameters, was also assessed.

(b) (4)

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

(b) (4)

3.2.P.5.2-5 and 3.2.P.5.3-5 Barrier Function

Method Summary

- The epidermal barrier function of each STRATAGRAFT final product designated for QC testing is assessed by (b) (4)
    - Barrier function is measured by (b) (4)

(b) (4)

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

(b) (4)

3.2.P.5.2-5 and 3.2.P.5.3-5 (b) (4) , Mycoplasma, Endotoxin, and Sterility (DBSQC Reviews)

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)

Review Comment: 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:

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 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
• 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

3.2.P.5.2. Analytical Procedure/Determination of (b) (4) : (MP)

The analytical method explained in Section 3.2.P.5.2. is a (b) (4)

Review of Method:

(b) (4)

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

(b) (4)

Mycoplasma (Drug Product) (SK)

Mycoplasma Test Qualification:

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

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

The Applicant 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) using (b) (4) lots of final product containing cells (i.e., (b) (4)) and (b) (4) cultivable mycoplasma strains, (b) (4) .

Review Comment: The composition of (b) (4) used in the (b) (4) method was not provided, therefore IR#3 was sent on July 9, 2020 to ensure (b) (4) as used in the method

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

Both (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 #3 and Review

The following question was sent in IR#3 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.

Endotoxin (Drug Product) (SK)

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

(b) (4) -BET utilizes (b) (4) methodology and (b) (4)

The Applicant qualified their (b) (4)-BET by testing (b) (4) to demonstrate their method is suitable under the actual conditions of use in accordance with (b) (4). The final product endotoxin sample is a (b) (4) sample containing (b) (4). For each tissue, (b) (4)

An (b) (4) test was performed where (b) (4). Based on the results, the Applicant proposed to test samples neat for release testing.

The Applicant 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).

Review Comment: The (b) (4)-BET test method is compliant with (b) (4).

Sterility (Drug Product) (SK)

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.

The Applicant qualified (b) (4) final tissue drug product using the (b) (4) method and (b) (4)

(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) . The original submission did not include (b) (4) to ensure initial (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,IR#3 and IR#10 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 (IR#3) and August 18 (IR#10), 2020 and responses were received on July 22 and September 2, 2020, respectively.

a. (IR3#)Sterility test qualification studies submitted under section 3.2.P.5.3 have test results of (b) (4) . However, additional information is needed; please

submit the initial (b) (4) results for all (b) (4) to ensure (b) (4) were below (b) (4) .

Review of the Response

The Applicant submitted (b) (4) results for all (b) (4) for both (b) (4) methods. The response was found acceptable.

b. (IR#10) 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

The Applicant submitted lot numbers for test samples used in the qualification studies. The response was found acceptable.

Review 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.

Container Closure Analytical Validation

Reviewer comment: Dr. Hector Carrero (CBER/OCBQ/DMPQ) reviewed the analytical procedure validation for container closure integrity.(LR)

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

- ❑ The finalized information provided is acceptable as submitted.
- ❑ The validation methods for Appearance, Histology, Barrier Function, (b) (4) , Sterility, Endotoxin, Mycoplasma were adequately performed to assure that methods are suitable for assurance of product identity, purity, and potency.
- ❑ There are no remaining deficiencies.

3.2.P.5.4 Batch Analyses (TT)

Batch release data is presented for (b) (4) lot size, (b) (4) lot size and (b) (4) lot size, together with (b) (4) process performance qualification lots manufactured using the commercial manufacturing process.

- All passed the lot release acceptance criteria except for (b) (4) size lot ((b) (4)), which failed viability testing ((b) (4)) and (b) (4) size lot ((b) (4)), which had a sterility failure.
  - Root cause investigations determined that the viability failure was likely due to the introduction of a (b) (4) of the tissue. This additional packaging was eliminated from subsequent lots. The sterility failure was likely due to the water reservoir of the tissue culture incubator being found to be contaminated with (b) (4).

3.2.P.5.5 Characterization of Impurities (TT)

A risk analysis on the ancillary materials likely to be present in the final product was performed and the results of theoretical calculations and quantitation of these residual components are presented.

Residual RSA and BSA

Rat serum albumin (RSA) is a known impurity in rat tail collagen, a starting material for the manufacture of STRATAGRAFT, and bovine serum albumin (BSA) is a component used in the (b) (4) .

- Immunoassays for RSA and BSA, using (b) (4) biopsies of final product, were quantified by comparison to standard curves.
  - Average BSA content was (b) (4) per 100 cm^2
  - Average RSA content was (b) (4) per 100 cm^2

Reviewer Comment: The package insert includes the language "Do not use in patients with known allergies to murine collagen or products of bovine or porcine origin".

(b) (4)

(b) (4)

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

(b) (4)

[redacted]

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

- The information provided is acceptable as submitted and support that manufacturing process and impurities are adequately controlled.
  - The information on Batch Analyses provides adequate support regarding consistency of the manufacturing process.
  - Impurities include rat and bovine serum albumin at low and acceptable levels. However, due to potential sensitives to such substances, the package insert includes the language "Do not use in patients with known allergies to murine collagen or products of bovine or porcine origin.
  - (b) (4) is used in manufacturing and could be a safety concern if present in the DP. IR #21 (09-23-2020) requested data to show the actual amount of (b) (4) present in the final product. On 09-28-2020 (Sequence 0017) the sponsor committed to determining the amount of (b) (4) in the product. However, on 11-6-2020 (Sequence 0025), the applicant provided the following information:
    - Evaluation of (b) (4)-based methods, using a homogenized final drug product sample, have been unsuccessful.
    - Stratatech is evaluating additional analytical techniques and will provide the data once a suitable analytical method has been developed.
    - While Stratatech hopes to submit this information for review during the BLA review period, a post-approval commitment may be required.
  - The risk assessments and available data suggest that (b) (4) levels are minimal and not likely to cause adverse events. The Applicant will provide the requested information as a PAS.

3.2.P.6 Reference Standards or Materials (TT)

The analytical methods used to test and release STRATAGRAFT do not utilize reference standards.

.

3.2.P.7 Container Closure System (LR)

The packaging components for the Hold Solution are described in **Table 56**. Letters of authorization to access information contained in the supplier drug master files are provided in Section 1.4.1 Letters of Authorization in the submission. The suitability of the packaging components is described in Section 3.2.P.2.4. The primary components are sterilized via (b) (4) at a qualified contract facility. Incoming packaging components are inspected for cleanliness, visual appearance, and dimensional attributes.

Reviewer comment: Dr. Hector Carrero (CBER/OCBQ/DMPQ) reviewed the sterilization information and integrity testing for the foil package for final DP and the bottle for Hold Solution and found it adequate to support licensure.

Table 56. Hold Solution packaging components.

Components			DMF No.
Bottle	Vendor	(b) (4)	(b) (4)
	Description	(b) (4) Injection Blow Molding	
	Material	(b) (4)	
	Sterilization Technique	(b) (4)	N/A
	Cross-Reference	Figure 1: StrataGraft Hold Solution Bottle Drawing	
Closure	Vendor	(b) (4)	(b) (4)
	Description	HDPE Injection Molding Resin (b) (4)	
	Vendor	(b) (4)	(b) (4)
	Description	(b) (4) white colorant 1%	
	Vendor	(b) (4)	(b) (4)
	Description	(b) (4) LDPE/HDPE Liner	
	Sterilization Technique	(b) (4)	N/A
	Cross-Reference	Figure 2: StrataGraft Hold Solution Cap drawing	
Label	Facestock	4 mil White Polyolefin	N/A
	Adhesive	(b) (4)	
	Ink	(b) (4) + resin ribbon	
Pouch	Vendor	(b) (4)	N/A
	Description	Laminated composite of nylon, aluminum foil, and an ethylene vinyl acetate copolymer sealant layer	
	Material	(b) (4) 60ga Nylon, 18 LDPE, 30ga aluminum foil, 14.4 LDPE, 1.5 mil LDPE-EVA	
	Sterilization Technique	(b) (4)	N/A
	Cross-Reference	Figure 3: StrataGraft Hold Solution Pouch drawing	

Reviewer comment: All cross-referenced Master Files are in CDER, with MF (b) (4) submitted in 2004, MF (b) (4) submitted in 1992, MF (b) (4) submitted in 1970, and MF (b) (4) submitted in 1975. Upon review of the CDER database (DARRTS), all the Master Files were cross-referenced by a number of submissions, including approved CDER BLAs, NDAs, and ANDAs, with some of the product names of the approved drugs shown below. There were no electronic submissions (paper

only) and no review memos in the database. However, the Applicant has provided sufficient information for review in the BLA regarding the container closure materials.

(b) (4)

A drawing of the Hold Solution bottle and cap are shown below:

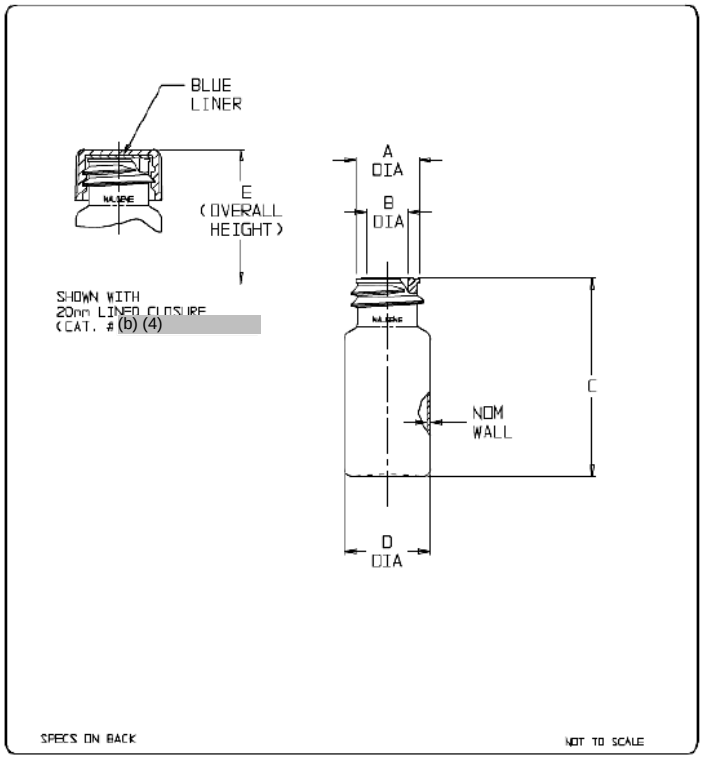


Figure 18. Hold Solution bottle and cap.

The packaging components of the STRATAGRAFT container closure system are summarized in **Table 57.** Letters of authorization to access information contained in the supplier drug master files are provided in 1.4.1 Letters of Authorization. The suitability (protection, safety, compatibility, and performance) of the packaging components are described in 3.2.P.2.4 Container Closure System. The primary components are sterilized via (b) (4) at a qualified contract facility. Incoming packaging components are inspected for cleanliness, visual, and dimensional attributes.

Table 57. StrataGraft container closure system packaging components.

Components			DMF No.
Product Dish	Vendor	(b) (4)	N/A
	Resin Vendor	(b) (4)	(b) (4)
	Description	(b) (4) Rectangular Tray	
	Material	(b) (4)	
	Sterilization Technique	(b) (4)	N/A
	Cross-Reference	Figure 1: Product Dish Drawing	
Insert/Membrane	Vendor – tissue insert	(b) (4)	N/A
	Vendor – tissue membrane	(b) (4)	N/A
	Description	100cm^2 Rectangular Insert	
	Material	Polycarbonate track-etched membrane sealed to a polystyrene molded frame	
	Sterilization Technique	(b) (4)	N/A
	Cross-Reference	Figure 2: Tissue Insert/Membrane Drawing	
Pouch	Vendor	(b) (4)	N/A
	Description	48ga PET, White LDPE, 0.35mil aluminum foil, LDPE, 2.0 mil Sealant Layer	
	Material	TPS-4051	
	Sterilization Technique	(b) (4)	N/A
	Cross-Reference	Figure 3: Tissue Pouch Drawing	

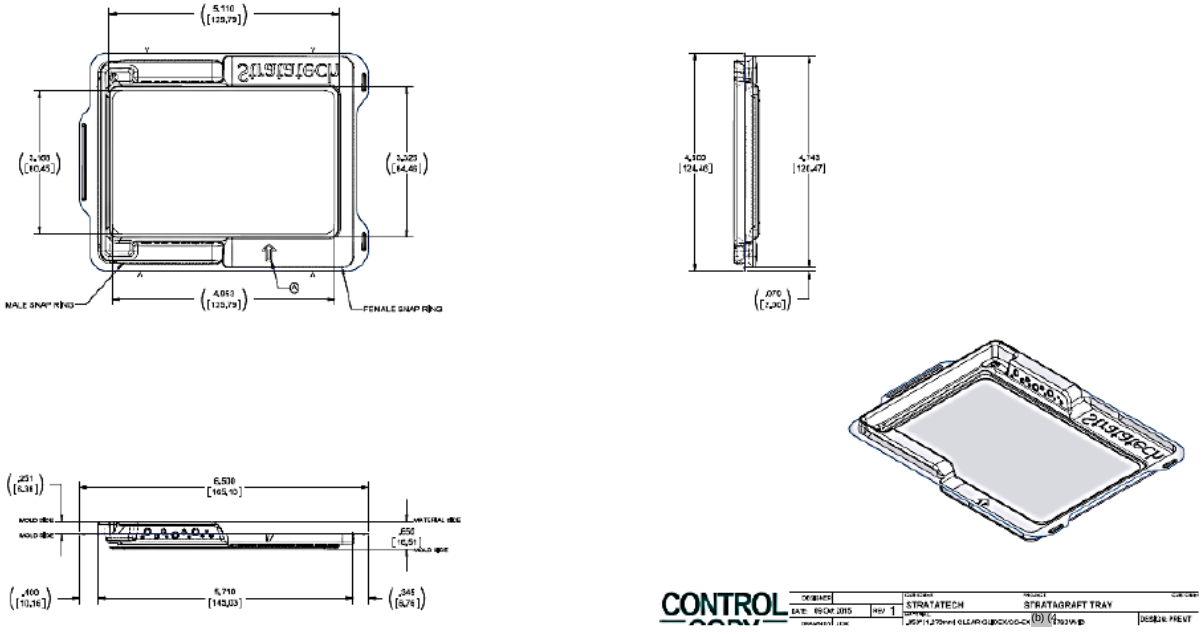
Reviewer comment: MF (b) (4) is in CDER and was submitted in 1993. Upon review of the CDER database (DARRTS), the Master File was cross-referenced by a number of submissions, including approved CDER BLAs, NDAs, and ANDAs as shown in the table below. There were no electronic submissions (paper only) and no review memos in the database. However, the Applicant has provided sufficient information for review in the BLA regarding the container closure materials.

MF	Examples of approved products cross-referencing MF

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

A drawing of the product dish and tissue insert/membrane are shown in **Figure 19**and **Figure 20**, respectively.

Figure 19. Product dish



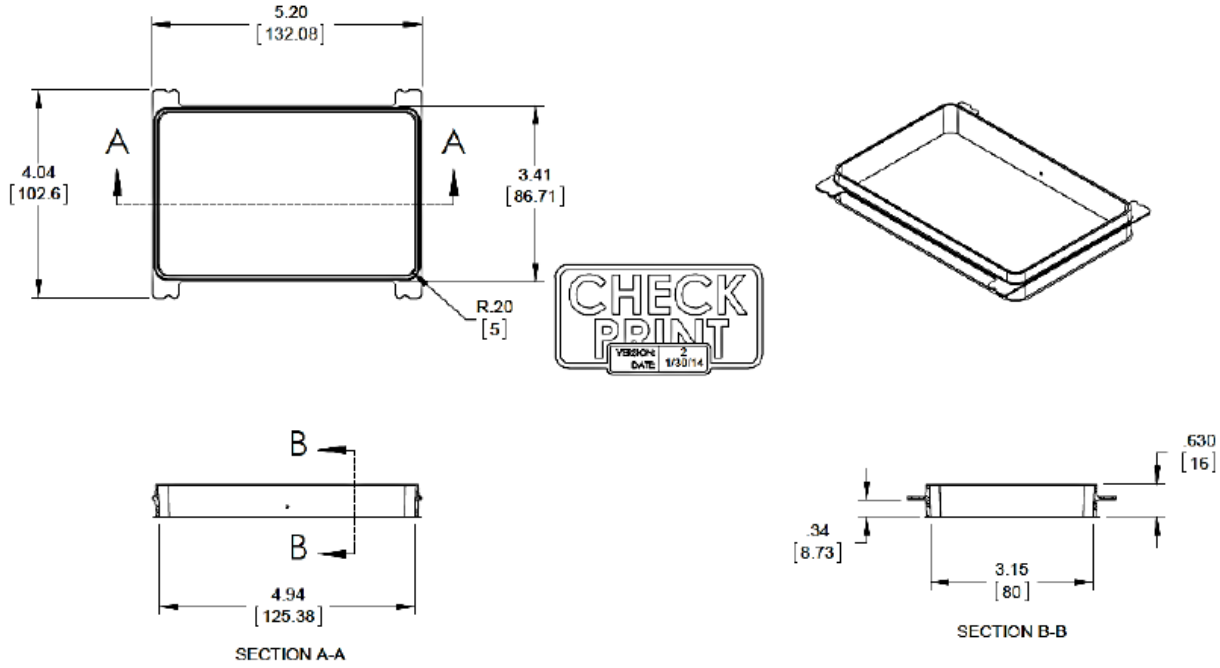


Figure 20. Tissue insert/membrane.

All components used in the packaging of STRATAGRAFT are all terminally sterilized via (b) (4) at (b) (4). Packaging components are (b) (4) at a target (b) (4), with (b) (4) located throughout each load to ensure adequate (b) (4) of all packaging components. The most recent operation qualification summaries for the (b) (4) load configurations, used to sterilize the packaging components for STRATARAFT, are provided as Attachment 1 and Attachment 2, respectively, in Section 3.2.P.7 (Container Closure System – Tissue) in the submission.

Sterilized components are received from the vendor with a Certificate of Compliance from the component vendor and sterilization site, assigned a lot number and inspected against established visual and dimensional acceptance criteria, as indicated in **Table 58** for Product Dish, tissue insert/membrane, and the tissue pouch.

Table 58. Product dish, insert/membrane, and pouch acceptance criteria.

Component	Test Method	Acceptance Criteria
Product Dish	Visual	• Pouches containing irradiated product dishes are free of rips, tears, punctures, slices or other obvious defects that have caused a breach in package integrity • Seal Visual Integrity Inspection (b) (4) pouch seals (of the pouches containing the product dishes) are free of channels, folds, voids, product caught in the seal, or other breaches of the sterile barrier
	Identity by (b) (4)	The (b) (4) matches that of the reference
	Dimensions	6.5 x 4.9 x 0.75" ± 0.25"
Insert/Membrane	Identity by FTIR	The (b) (4) matches that of the reference
	Dimensions	5.2 x 3.4 x 0.63" ± 0.25"
Pouch	Visual	• Outer pouch containing the irradiated product pouches are free of rips, tears, punctures, slices or other obvious defects that have caused a breach in package integrity
	Dimensions	10.25 x 6.75" ± 0.25"

Vendor test reports for the Product Dish, Tissue Insert/Membrane, and Pouch are provided in Attachment 3, Attachment 4, and Attachment 5, respectively, of Section 3.2.P.7 (Container Closure System – Tissue) in the submission. Attachment 3 contains a letter from the vendor of the product dish which states that the raw materials used in the manufacture of the (b) (4) additive for (b) (4) may contain materials derived from (b) (4) sources. These (b) (4) sources do not originate in the countries where BSE has been diagnosed. The processing conditions were provided.

Reviewer comment: It is this reviewer's opinion that the information provided about the TSE/BSE risk for the (b) (4) is acceptable.

Attachment 4 contains a summary of validation testing for the tissue insert/membrane from the vendor. All components were verified to be animal free.

Attachment 5 contains information on the tissue pouch from the vendor ((b) (4)). Certain raw materials used in the manufacture of some (b) (4) products do contain animal derived material; specifically (b) (4) . The suppliers of the raw materials have indicated that processing conditions meet or exceed the recommended conditions by (b) (4) . As such, to the best of their knowledge, (b) (4) products do not contain substances having the risks of transmitting BSE/TSE.

- Reviewer comment: It is this reviewer's opinion that the information provided about the tissue pouch, including the TSE/BSE risk, is acceptable.

Overall Reviewer's Assessment of Section 3.2.P.7:

- The container closure information is acceptable as submitted.
- No deficiencies were identified.

3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data HOLD SOLUTION (LR)

A hold time evaluation for one batch of Hold Solution (Lot (b) (4)) has been completed up to 6 months at 2-8ºC and (b) (4) on material stored in the horizontal orientation. The Hold Solution was manufactured and filled at commercial scale and packaged into the configuration as described in section 3.2.P.7.1 Container Closure System – Hold Solution. The Hold Solution bottles tested were not placed into the laminated foil pouch, thus representing a worst-case configuration in terms of potential (b) (4) . The test protocol for the evaluation of the Hold Solution is shown below.

.

Table 59. Hold Solution stability test protocol

Test	Acceptance Criteria	Time points (Months)
(b) (4)		T0 (release), 3, 6, 9, 12, (b) (4) months
		T0 (release), and (b) (4) months
		QC Release

a Sterility testing may be performed at an earlier time point in the event of an out of specification to establish sterility at the final time point.

Summary of the test results:

(b) (4)

The Applicant has proposed an expiry period of 12 months for the Hold Solution. They state they will continue to collect additional stability data and that extension of the expiration dating of the Hold Solution may be possible if acceptable full term stability data are generated on the stability lots. If this occurs, the Applicant will provide the agency with a revised expiration dating recommendation along with supporting stability data.

Reviewer comment: The Applicant has only collected stability data to support a 6 month shelf-life for the Hold Solution. Thus, it is not clear why the Applicant is proposing a 12 month shelf-life. Additionally, sterility testing should be performed on the final time point for which shelf-life is being claimed. The Applicant was sent Information Request #9 on August 18, 2020 and provided their responses on September 2, 2020 in Amendments 9 and 16. The Applicant provided stability data out to 12 months, with all results being acceptable. Currently the Applicant has only provided stability data for Lot (b) (4) of the Hold Solution. In response to Information Request #23, dated October 5, 2020, the Applicant stated that the Hold Solution is designated as an excipient and they plan on placing the (b) (4) commercial lots of Hold Solution on stability.

In Section 3.2.P.3.5-2 Transportation Studies, the sponsor describes transportation validation studies of the Hold Solution and Hold Dishes. Pouched Hold Solution bottles and Hold Dishes were incorporated into the study to simulate the minimum and maximum shipment loads. An (b) (4) temperature profile simulation study was performed for (b) (4) conditions, which were run (b) (4) to achieve a (b) (4) evaluation. In addition to evaluating the packaging components, the hold solution was evaluated for (b) (4) . All criteria were met for the (b) (4) profile studies.

Reviewer comment: Dr. Hector Carrero (CBER/OCBQ/DMPQ) reviewed the transportation studies and found that they were adequate to support licensure.

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

STABILITY SUMMARY AND CONCLUSION

Stability evaluations have been completed up to 12 months for development ((b) (4) -unit scale) and commercial ((b) (4) unit scale) batches and for (b) (4) PPQ batches held for three months held at -70 to -90ºC. **Table 60** provides a list of STRATAGRAFT lots in stability studies. Data for each of these lots is provided in section 3.2.P.8.3 Stability Data.

Stability samples were held in the final packaging (described 3.2.P.7.1 Container Closure System – Skin Tissue) consisting of 100 cm^2 Tissue Insert within a (b) (4) product dish, which is heat-sealed in a laminated foil pouch.

Table 60. Summary of stability lots of StrataGraft manufactured through initial PPQ

Lot Number	Manufacturing Site	Tissue Scale	Date of Manufacture	Time Intervals Completed (months)
(b) (4)	Stratatech Corp.	(b) (4)		0, 3, 9, 12
	Stratatech Corp.			0, 3, 9, 12
	Stratatech Corp			0, 3, 9, 12
	Stratatech Corp.			0, 3, 6, 9[a]
	Stratatech Corp.			0, 3, 6, 9[a]
	Stratatech Corp			0, 3, 6, 9[a]
	Stratatech Corp			0, 3, 6, 9, 12
	Stratatech Corp			0, 3, 6, 9, 12
	Stratatech Corp			0, 3, 6, 9, 12
	Stratatech Corp			0, 3, 6, 9, 12
	Stratatech Corp			0, 3, (6, 9, 12, (b) (4))
	Stratatech Corp			0, 3, (6, 9, 12, (b) (4))
	Stratatech Corp			0, 3, (6, 9, 12, (b) (4))

( ) Pending Time Points in Parenthesis

a Stability studies terminated after the 9 month time point due to an Out of Specification. These lots were not incorporated into the stability evaluation.

The stability samples were evaluated using validated analytical methods for appearance, histology, viability, (b) (4) , and sterility. Acceptance criteria for stability studies are located in 3.2.P.5.1 Specifications. Analytical procedures are described in 3.2.P.5.2 Analytical Procedures. (b) (4) lots manufactured at the (b) (4) -lot scale in (b) (4) were not incorporated in stability evaluation. For these lots, some of the biopsy samples ((b) (4) were taken from each tissue for viability) failed to meet specifications at 3, 6, or 9 months. Investigation concluded this was due to tissue handling and storage conditions after drug product manufacture. The stability study for these three lots was terminated after the 9-month time point and corrective actions were incorporated.
(b) (4) subsequent lots at the (b) (4) -unit scale were included in stability studies and were used in clinical trials ((b) (4)).

Results

- Appearance: all results at all test intervals met the acceptance criterion.
- Histology: All results at all test intervals met the acceptance criterion.

- Viability: All results at all test intervals met the acceptance criterion. Trend analysis of data to 12 months by fit to a multiple regression model indicated that the viability would exceed the minimum release criteria out to (b) (4) months (95% confidence).
- (b) (4) : All results at all test intervals met the acceptance criterion. Trend analysis of data to 12 months by fit to a multiple regression model indicated that (b) (4) would exceed the minimum release criteria out to (b) (4) months (95% confidence)
- Sterility: All batches tested up to 12 months met the acceptance criteria.

Shelf Life Period and Labeled Storage Condition

STRATAGRAFT is currently assigned a shelf life of 12 months based on completed stability studies completed to date. These data support the label statement of a 12-month shelf life when the product is stored at or below -80^{0}C.

Upon completion of stability studies on (b) (4) lots manufactured at the (b) (4) -tissue lot size for the PPQ, the final product shelf life will be evaluated. Stratatech may provide relevant data and analysis to propose extension of the shelf-life based on this evaluation.

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

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment: HOLD SOLUTION (LR)

Stratatech commits to continue the ongoing stability studies for the Hold Solution. In addition, the first two commercial lots of Hold Solution will be placed on stability. The post-approval protocol includes testing of samples stored at the recommended storage condition of 2 - 8°C and the assays reflect those tests and acceptance criteria currently used to assess stability of the Hold Solution. The post-approval marketed stability protocol for the Hold Solution is shown in Table 61 below.

Table 61. Post-approval marketed product stability protocol the Hold Solution

Test	Time Intervals (Months)					
	0	3	6	9	12	(b) (4)
(b) (4)	x	x	x	x	x	
	x	x	x	x	x	
	x	x	x	x	x	
	x	--	--	--	x	
	x	--	--	--	--	

a Sterility testing may be conducted between the 12-month (b) (4) time points to establish an extended shelf life

x Test performed at this time point

-- No testing performed at this time point

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment: STRATAGRAFT

The applicant commits to continue the ongoing stability study of the (b) (4) PPQ lots out to (b) (4) months as described in section 3.2.P.8.1 Stability Summary and Conclusion. In addition, one batch of STRATAGRAFT will be placed on stability (b) (4) at either the (b) (4) -tissue or the (b) (4) -tissue scale. The post-approval stability protocol is presented in Table 62 below.

Table 62. Post-Approval Marketed Product Stability Protocol for StrataGraft

Test	Time Intervals (Months)					
	0	3	6	9	12	(b) (4)
Skin Tissue Appearance	x	x	x	x	x	
Tissue Uniformity and Histology	x	x	x	x	x	
(b) (4)	x	x	x	x	x	
Tissue Viability	x	x	x	x	x	
Sterility[a]	x	--	--	--	x	
Container Closure Integrity	x	--	x	--	--	

a Sterility testing may be conducted between the 12-month (b) (4) time points to establish an extended shelf life

x Test performed at this time point

-- No testing performed at this time point

Overall Reviewer's Assessment of Section 3.2.P.8:

- The information provided to date support the proposed shelf-life of 12 months for both the Hold Solution (stored at 2-8^{0}C and for STRATAGRAFT final product (stored at -70 to 90^{0}C. Post-approval commitments are adequate and may provide sufficient information to allow extension of the shelf-life for both Hold Solution and the STRATAGRAFT final product
- For the DP, stability evaluations have been completed up to 12 months for development ((b) (4) unit scale) and commercial ((b) (4) -unit scale) batches and for (b) (4) PPQ batches held for three months held at -70 to -90ºC. This data supports the proposed 12-month shelf-life.
- For Hold Solution, there was one deficiency.
  - The Applicant was sent Information Request #9 on August 18, 2020 and asked to provide additional stability data to support a 12-month expiry period for the Hold Solution. The Applicant provided the requested information on September 2, 2020 and September 28, 2020 in Amendments 9 and 16, respectively. The information provided by the Applicant is acceptable.
  - The Applicant was sent Information Request #23 on October 5, 2020 and asked to provide stability data for additional lots of the Hold Solution. The Applicant provided a response on October 9, 2020 in Amendment 19 and stated that the Hold Solution is designated as an excipient and they plan on placing the (b) (4) commercial lots of Hold Solution on stability. The information provided by the Applicant is acceptable.
- No remaining deficiencies that should be included in a CR letter.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

This section of the BLA was reviewed by Hector Carrero DMPQ. There were no deficiencies that would preclude licensure based on review of the information in the BLA. A PLI was conducted May3-7, 2021. No objectionable conditions were noted.

Overall Reviewer's Assessment of Section 3.2.A.1:

- I agree with DMPQ reviewer Hector Carrero that the information provided is acceptable as submitted.
- A PLI was conducted May3-7, 2021. No objectionable conditions were noted.

3.2.A.2 Adventitious Agents Safety Evaluation (TA)

Review of Module 3 section 3.2.A.2, Adventitious Agents Safety Evaluation, focused on information covering Control of raw materials of biological origin, Viral and adventitious agent testing of the (b) (4) drug product testing for sterility and mycoplasma. The reviewer confirmed that all of the biological raw materials, (b) (4) DP are adequately tested for microbial safety as per the (b) (4) guidelines and FDA guidance. All of the safety-test assays are performed and validated by contract manufacturing organizations or vendors. Relevant assay validation reports are submitted to the file and reviewed. From a viral and adventitious agents safety perspective, the provided information is complete and supports licensing of the STRATAGRAFT product.

STRATAGRAFT is a biologically active tissue construct which cannot undergo terminal sterilization or virus clearance methods for the final product. The following strategy was used to assess (b) (4) drug product for viral adventitious agents.

- Control of raw materials of biological origin.

(b) (4)

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

(b) (4)

- **Viral Clearance Studies**

Overall Reviewer's Assessment of Section 3.2.A.2:
Initially, the submitted information was incomplete because there was inadequate information on performance and validation by the CROs that perform adventitious agent testing. Also, there was inadequate information on viral clearance during manufacturing of the (b) (4). Several IRs were issued and there was discussion about this topic at the Mid Cycle and Late Cycle meetings to address these issues. Due to the lack of Master Files for all of the adventitious virus testing by CROs, FDA accepted relevant validation reports by e-mail from the vendors on behalf of the Applicant. Most of the information pertaining to Module 3 section 3.2.A. 2 is complete and acceptable. However, as of 1/20/2021, there are remaining questions regarding viral clearance during manufacturing of rat tail collagen. The studies performed to date were inadequate either to flawed study design or inability of the current (b) (4) manufacturing process to inactivate of clear model viruses to current expectations. The cause and resolution remain to be determined but will be the subject of a CMC safety-related PMR. Overall, this lack will not be considered sufficient to warrant a CR since Stratatech has other controls in place to (b) (4) Nonetheless, as a Post-Marketing Requirement (PMR), Stratatech should conduct a more adequate viral inactivation study to more accurately quantify the (b) (4) manufacturing process and to ensure the safety of the product.

- The following deficiencies were identified, and applicant was sent information request (IR) via email to address the deficiencies:
    - The information on safety evaluation of raw materials such as BSA, (b) (4), and Trypsin, was inadequate.
    - There is no information on validation of the assays that were used to evaluate the safety of MCB, WCB and rat tail collagen.
    - There is no validation report of the assays used to tests safety of the cells, which were cultured in media having BSA, for bovine-tropic viruses, in accordance with 9 CFR parts 113.46, 113.47.
    - There was no information regarding viral clearance during manufacturing of (b) (4).
- Specifically, three IRs were sent to applicant in regard to matters related to Module 3.2.A.2:
    1. IR#15was sent on 9/10/2020 and a reply received on September 22, 2020 (sequence 0016). The request noted that information on safety of raw materials such as (b) (4), BSA, and Trypsin were incomplete and requested complete information. Regarding BSA, applicant replied that a COA for a recent lot of the BSA, (b) (4), was provided to section 3.2 A.2. In addition to (b) (4) documenting the testing of the serum in accordance with 9 CFR 113.53 and are in compliance with the requirements for ingredients of animal origin as shown on the CoA. In regard to (b) (4), applicant confirmed that the Purified BSA is the only bovine material used to formulate the (b) (4) solution. Therefore, the BSA used to prepare the (b) (4) is also certified as mentioned here above and CoA is submitted to the BLA file.

       The IR #15 also noted that the COAs on Trypsin did not show that it was adequately tested for the absence of (b) (4). As discussed during CRMTS #11998 (October 15,

2019), the applicant notified the agency that any further information on the cell stocks, including (b) (4) is no longer maintained by (b) (4) . Thus CoAs for the Trypsin used to manufacture the (b) (4) are not available. It was noted that applicant has been using Trypsin solutions from different sources ((b) (4)), but not all of the CoAs state the Trypsin is tested in accordance with 9 CFR. In response Stratatech provided showing the Trypsin lots are tested as required in 9 CFR 113.53. Also, (b) (4) Trypsin lots from (b) (4) have been (b) (4) . The Applicant provided data to show that this was adequate to provide inactivation of (b) (4) .

Conclusion: The questions in IR #15 were satisfactorily addressed by the applicant.

2. IR#14; 9/20/2020: The Agency requested that the applicant provide complete validation reports for viral screening and detection methods used for Adventitious Agent and Viral Testing of (b) (4) . A reply was received on September 30, 2020. (sequence 0018). Many of the specification tests performed for the (b) (4) as well as methods for adventitious agent and viral testing of (b) (4) are performed by contract laboratories, primarily (b) (4) . Stratatech requested the relevant validation reports from the vendors. (b) (4) submitted the validation reports directly to the Agency.

   Conclusion: On behalf of the Applicant, the vendors submitted the validation reports for each type of tests performed to evaluate the safety of the (b) (4) . All of the validation reports are performed following guidelines or guidance provided in (b) (4) and FDA. Therefore, the validation reports were complete and are acceptable.

3. IR#35; On 11/13/2020, Agency requested that the applicant provide validation reports on the assays used to test the safety of the biological materials that have contact with BSA, for (b) (4) as per 9 CFR. The response was emailed directly to the FDA by the contract manufacturing organization, (b) (4), on November 17, 2020.

   Conclusion: The validation report is performed in accordance with the guidance documents of ICH and FDA on validation of assays.

   Overall, the information on adventitious virus testing is sufficient to support licensure of STRATAGRAFT.

- As of 2/3/2021, there are remaining questions regarding viral clearance during manufacturing of rat tail collagen. The rat tail collagen type I presents a potential, but very small risk of transmission of adventitious virus which could result in a serious adverse event (SAE). Currently, the Sponsor is deficient in their viral clearance study by only achieving a (b) (4) clearance for (b) (4) model viruses (> 6 log 10 is current recommendation). Additionally, the study was flawed in that there was only (b) (4) in (b) (4) before the study was performed. Overall, this lack will not be considered sufficient to warrant a CR since this RMAT product addresses an unmet medical need and the Applicant has other controls in place to mitigate the risk of rat-specific viral transmission, including monitoring and pathogenic testing of the closed rat colonies, lot release adventitious agent testing of the collagen, enhanced pharmacovigilance monitoring, and no reported adverse events related to rat-specific viral infection. To further evaluate the potential of an unexpected

serious risk, the Applicant will be required to conduct a viral clearance study as a Title IX PMR. This would demonstrate clearance of model viruses Parainfluenza virus type 3 (PI3), Pseudorabies virus (PRV) and Murine Minute Virus (MMV). The Sponsor would need to show a clearance level of >6 log 10 for all viruses. ❑ On 2/4/2021, the Applicant was sent an e-mail informing them that there were concerns about the adequacy of the viral clearance study and requesting discussion about this issue with a response from them by no later than 2/10/2021.

3.2.A.3 Novel Excipients

Please refer to review of 3.2.P.4.6 Novel Excipient

3.2.R Regional Information (USA)
Executed Batch Records

Master Batch records were included in amendment 28 (Sequence 0029) received 11/20/2020.
The original BLA submission includes executed batch records at both the (b) (4) -tissue and (b) (4) -tissue lot size. (b) (4) (registration lot) was made at the (b) (4) -tissue scale and (b) (4) (PPQ lot) was made at the (b) (4) -tissue scale. Both lots were manufactured at the Stratatech Facility in Madison Wisconsin.
Review Comments: The executed batch records include reference to all relevant SOPs, data from each manufacturing step, information on equipment calibration, and appropriate QC notes and clearance. Operators are clearly instructed to contact management if QC tests or operating ranges for volumes/times/ or other crucial parameters are not as expected and defined. Future changes to the Master Batch record will be needed to incorporate changes to barrier function and histology methods which were updated during review of the BLA.
The executed Batch records indicate that manufacturing is well controlled at the Stratatech Facility in Madison Wisconsin.

Method Validation Package (TT)
Please refer to section 3.2.P.5.3 for validation of analytical procedures. According to 21 CFR 610.2(a), Stratatech may be required to provide samples of STRATAGRAFT batches for the CBER lot release program. However, the FDA has determined that STRATAGRAFT will not be evaluated for batch release. The method validation reports have been submitted and batch samples will be submitted only upon request.

Comparability Protocols
No formal product comparability protocols have been submitted. Manufacturing changes at the Stratatech Facility in Madison Wisconsin will be addressed through BLA supplements.
Review Comment: the applicant conducted comparability studies through (b) (4) different process development stages as reviewed in Section 3.2.P.2.3 Manufacturing Process Development above. In addition, an extensive report on CMC comparability of product manufactured in each process and related clinical outcomes data is presented in Section 5.4. It is entitled “STRATAGRAFT SKIN TISSUE ASSESSMENT OF THE CLINICAL COMPARABILITY OF THE STRATAGRAFT

SKIN TISSUES USED IN THE STRATA2011 AND STRATA2016 CLINICAL STUDIES: If further changes to manufacturing are needed, product characteristics and assessments as reported in Section 3.2.P.2.3 and 5.4 could be incorporated in future BLA supplements. The comparability studies were well designed and would likely be adequate to assess comparability subsequent to future changes.

3.2.R StrataGraft Xenotransplantation Exemption

Summary

Sponsor Request: In Section 3.2.R.4 Stratatech included a request for "exemption from the FDA xenotransplantation requirements, including a full exemption from donor deferral and passive monitoring for patients who are treated with STRATAGRAFT." The request was made because the StrataTech product, StrataGraft, is no longer made using mouse feeder layers. However, the human keratinocyte cell line used in manufacturing of the product originated on mouse feed cells and the keratinocyte master cell bank was made using the (b) (4) .

Current requirements: Based on the FDA Guidance Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (December 2016), sponsors and license holders of xenotransplantation products should archive appropriate samples (pretreatment blood samples for follow-up and reserves for the PHS) for up to 50 years and follow recommended procedures for health records and data management. These recommendations include all xenotransplantation-related information, including procedures, a description of the xenotransplantation product, and any xenotransplantation product-related adverse events. In addition, sponsors should develop an appropriate tracking system for all recipients of their xenotransplantation products and use this tracking information to facilitate notification in the case of a serious adverse event related to a xenotransplantation product. In addition, appropriate deferrals from blood and tissue donation for recipients and their intimate contacts should be considered.

Risk assessment: Potential xeno-related risks for this product are likely lower than current xenotransplantation skin replacement product Epicel, marketed under an HDE. Epicel uses mouse 3T3 cells during manufacturing, whereas StrataGraft does not currently use any mouse feeder cells. There have been no reported public xenotransplantation health concerns with Epicel and none have been reported for StrataGraft, which has been used in clinical trials for more than 15 years. Based on the extensive cell-line testing for xeno-related viruses (including deep sequencing), lack of detectable mouse DNA in the product, and lack of clinical concerns regarding xeno-related adverse events, StrataGraft seems to present less of a risk than Epicel.

In addition, Sequence 0015 in response to IR 18 has information showing that DNA from the allogenic cell lines NHDF and NIKS is not detectable at 3 months after product placement on wound sites.

Also, due to the xeno-related nature of STRATAGRAFT, the pharmacovigilance plan includes expedited reporting for adverse events possibly related to xenotransplantation.

Proposal for xeno-compliance for StrataTech. We recommend that STRATAGRAFT continue to be designated as a xenotransplantation product but that the sponsor need not follow all xenotransplantation recommendations. We conducted a risk analysis and consider their product to have relatively low risk compared to the only currently approved xenotransplantation product, Epicel. Epicel also does not follow all of the relevant recommendations in current xenotransplantation guidance. Based on this risk analysis, we propose to initially model our xenotransplantation recommendations based on what was required for Epicel.

On December 18, 2020 we sent the Applicant a letter denying their request for exemption. The following comments were conveyed in the letter:

1. Stratatech will archive samples of the final product from every other lot.

2. Stratatech will obtain baseline, i.e., pre-treatment, samples of the patient's blood for archiving in accordance with the FDA Guidance for Industry, Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans (2016), available at: https://www.fda.gov/media/102126/download.

3. STRATAGRAFT recipients, but not their intimate contacts, should defer from donating whole blood, blood components, source plasma, source leukocytes, tissues, breast milk, ova, sperm, or other body parts for use in humans.

4. The Prescription Information (PI) and patient instruction sheet will communicate to the patient, or through the treating physician, the xenogeneic nature of STRATAGRAFT.

5. Stratatech will ensure that the patient's medical record indicates that the patient has been treated with a xenotransplantation product. The record will state: This patient has been treated with STRATAGRAFT (allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen - dsat), a product manufactured with human cells previously exposed to murine cells.

6. The patient instruction sheet will communicate to the patient and through the treating physician that the patient should consider allowing an autopsy examination of their body upon death.

7. Stratatech will maintain a database to collect STRATAGRAFT patient and product information. This information will be provided to the FDA in the periodic safety reports (Periodic Adverse Experience Reports(PAERs)) at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals ((21CFR 600.80(c)(2)). The information will include:

   a. Patient: full name, date of birth/age,

   b. Treating hospital: name, address, designated hospital contact name and phone number,

   c. Treating physician: full name, phone number, practice name and address (if different from the treating hospital),

   d. Primary care physician (PCP): name, address and phone number,

   e. Information regarding the storage and analysis of patient and product- associated archival materials (e.g., pre-treatment and product lot samples),

   f. Information on patient follow-up,

   g. Notification of patient's death, including cause of death (if applicable).

8. Stratatech will provide expedited adverse event reports within 15 days to FDA regarding dermatological malignancy(ies), unexpected infection and any clinical events that are suspicious of a xenogeneic cause.

9. STRATAGRAFT recipients will be passively monitored. Stratatech will conduct active investigation of any suspicious clinical events reported to Stratatech.

In Amendment 34 the Applicant requested the following changes regarding product and patient sample archiving
Archiving of product: due to the source of xenogeneic concern arising from the historical use of (b) (4) feeder cells during NIKS MCB manufacture, the Applicant is proposing to archive the (b) (4) feeder cells used to manufacture the NIKS MCB and every lot of NIKS WCB in lieu of final product sample archiving.
Archiving of patient samples: The Applicant proposes to collect and archive baseline blood samples containing stabilized ribonucleic acid (RNA) in lieu of the archival plasma and leukocyte samples noted in the FDA and PHS Guidance.
Reviewer comment: these changes are acceptable.

During a teleconference with the APPLICANT on 05 Feb 2021, it was agreed that the approach proposed in 1.11.4 Sequence #0034 for the collection and archiving of pre-treatment patient baseline blood samples was suitable to comply with the Agency's requirement #2 in the Xenotransplantation Exemption Denial Letter. During the meeting, the Agency requested that the process for the approach be supplied to the review team. The process is detailed below:
1. As part of the surgical consent process, the patient will be provided with the Patient Information Sheet and made aware that a blood sample will be drawn for long-term storage in the event future xenotransplantation testing is required.
2. Obtain one (b) (4) Blood RNA Tube and apply patient-specific label.
3. Ensure the patient-specific code is captured on the patient and product capture form.
4. Draw blood directly into the (b) (4) Blood RNA Tube according to manufacturer recommendations and institutional standard procedures.
5. Immediately after the blood collection, shake the tube vigorously to ensure the stabilizing reagent is thoroughly mixed with the blood sample
6. Transfer the (b) (4) tube containing the stabilized blood sample to refrigerated storage until shipment. Shipment to the central repository for archival storage is to occur within (b) (4) days of sample collection.
7. Ship (b) (4) tube containing the stabilized blood samples via overnight delivery to the 3rd party vendor identified in the instructions provided with the laboratory supply kit being sure to follow all instructions provided. Ship the sample in an insulated shipper containing cold packs and according to your institutional procedures for shipment of medical samples.
8. Once received, the sample will be logged and stored in an ultracold freezer by the 3rd party vendor.

Review comment: this approach is acceptable.

Other eCTD Modules
Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

The Applicant claims categorical exclusion from the requirement to provide an environmental assessment under 21 CFR 25.31(c).

The applicant provided the following justifications: (1) the application does not significantly alter the concentration or distribution of the substance, its metabolites, or degradation products in the environment; (2) the cells, collagen, and components of tissue culture ((b) (4)) are naturally occurring substances; (3) the cellular components of STRATAGRAFT have stringent nutritional requirements for survival and replication and are therefore not viable in the environment; (4) none of the cellular and noncellular components of STRATAGRAFT have been subjected to genetic modification; and (5) no extraordinary circumstances exist, which may significantly affect the quality of the human environment and would thus require the preparation of an Environmental Assessment.

Reviewer comment: The applicant's justifications and the rationale for claiming categorical exclusion under 21CFR 25.31 (c) from the need to prepare an environmental assessment are acceptable.

B. Labeling Review

Full Prescribing Information (PI):

Review Comment: Final Prescribing Information and Patient Information Sheets were provided by the Applicant in Amendment 48 (Sequence 46) submitted 4/6/2021. Acceptable changes were subsequently made:

- Amendment 50 Sequence 49: USPI and Patient Information Sheets versions without dates were submitted at FDA's request.
- Amendment 52 Sequence 51: A minor typographical error was identified and corrected within the final patient information sheet that was submitted to the BLA in Sequence #0049 on 20 May 2021. This error occurred within the zip code for the Stratatech facility in Madison, WI.

Dosage Form and Strength: STRATAGRAFT is an off-white, rectangular sheet of approximately 100 cm^2 (approximately 8 cm by 12.5 cm), consisting of a viable, bioengineered, allogeneic cellularized scaffold product derived from keratinocytes grown on gelled collagen containing dermal fibroblasts.

Description: This section of the PI describes the nature of the product (bioengineered skin construct), its manufacturing, and that manufacturing includes reagents of animal origin including rat-tail collagen type I, calf serum, porcine trypsin and purified bovine serum albumin. The label briefly describes the packaging of the product and that it is supplied with a polycarbonate supportive membrane insert, a Hold Dish, and Hold Solution. The Hold Solution is a cell-culture medium that is not supplemented with growth factors.

The PI also explains why STRATAGRAFT is considered to be a xenotransplantation product although no xenogeneic cells are currently used in manufacturing.

Clinical Pharmacology: This section of the PI comments on STRATAGRAFT's proposed mechanism of action based on its nature as an allogeneic cellularized scaffold product containing metabolically active cells that produce and secrete a variety of growth factors and cytokines which

may help healing. STRATAGRAFT does not remain permanently engrafted, but is replaced by the patient's own cells over time, reducing the need for autografting to attain definitive closure of the majority of treated wounds.

How Supplied/Storage and Handling: This section of the PI STRATAGRAFT describes the construct that is loosely adherent to a polycarbonate membrane within a polystyrene frame and packaged in an aluminum foil vacuum sealed foil pouch contained within a carton.
STRATAGRAFT is shipped on dry ice and is stored between -70°C and -90°C. The Hold Solution is stored between 2°C and 8°C and Hold Dishes are stored at ambient temperature.
Unused STRATAGRAFT and materials that have come into contact with STRATAGRAFT should be disposed of as surgical biohazardous waste in accordance with local requirements.

Carton and Container Label:

Final labels were submitted in Amendment 49, sequence 0047 (4/30/21) A typographical error was corrected in Amendment 51 (sequence 50) on 5/24/21An error in the carton label was corrected in Amendment 56 (sequence 55) on 6/10/21.

Primary Pouch Label: This is the label on the outside of the foil pouch containing cryopreserved STRATAGRAFT

NDC 73612-200-01 **Rx Only**

allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat

STRATAGRAFT®

Store at -70° to -90°C (-94 to -130°F)

Manufactured and distributed by:
Stratatech Corporation
510 Charmany Drive, Suite 150
Madison, WI 53719
ph. 1-877-647-2239
U.S. License Number: 2144

Ref: SPC-FP-0788
Lot:
Exp:

See Full Prescribing Information for additional information.

3 73612 20001 5

Contains 1 Construct

TPL-LBL-0001 Rev.7

Primary Carton Label: This is the carton that contains the pouch with product.

Hold Dish Tissue Tray Label: This is the label for each Hold Dish tissue tray:

allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat

STRATAGRAFT® Hold Dish

For use with STRATAGRAFT

Store at ambient temperature.

See Full Prescribing Information for additional information.
STERILE. Do not open until immediately prior to use.

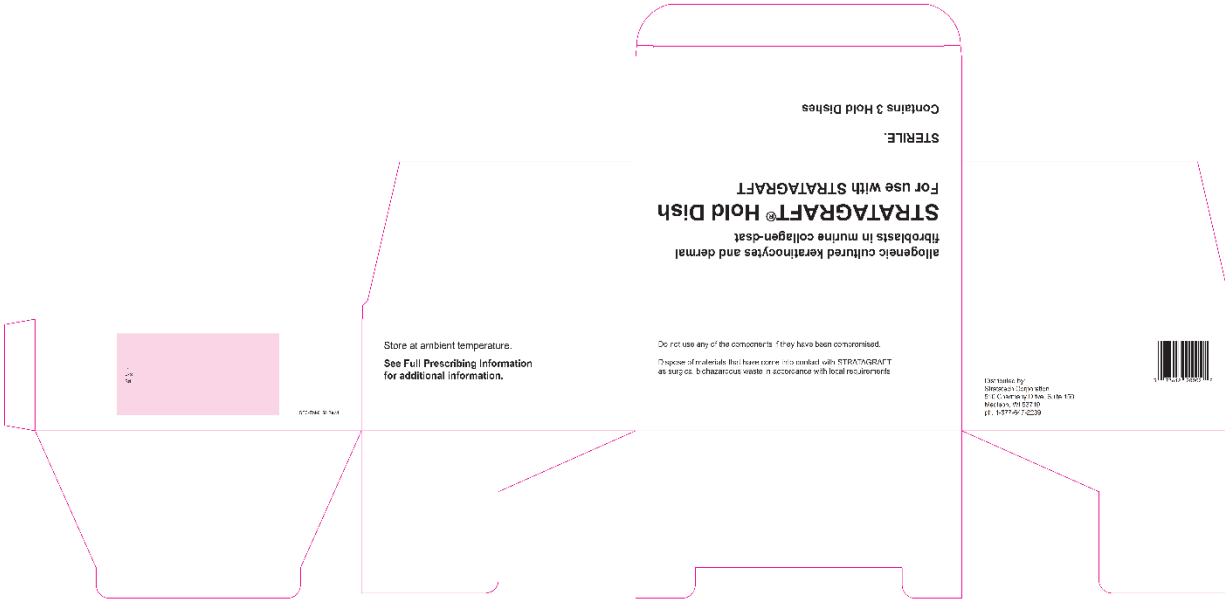
Distributed by:
Stratatech Corporation
510 Charmany Drive, Suite 150
Madison, WI 53719
ph. 1-877-647-2239

3 73612 20002 2

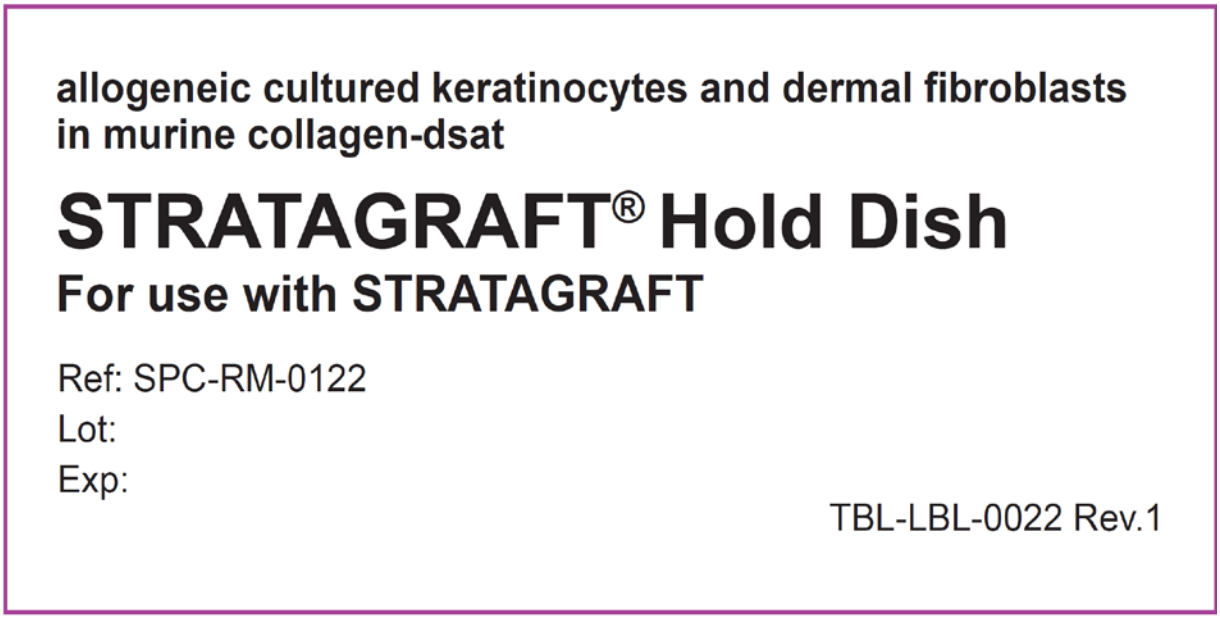
Ref: SPC-RM-0122
Lot:
Exp:

TPL-LBL-0020 Rev.1

Hold Dish Tray Carton Box: This is the label for each box that contains 3 Hold Dishes:



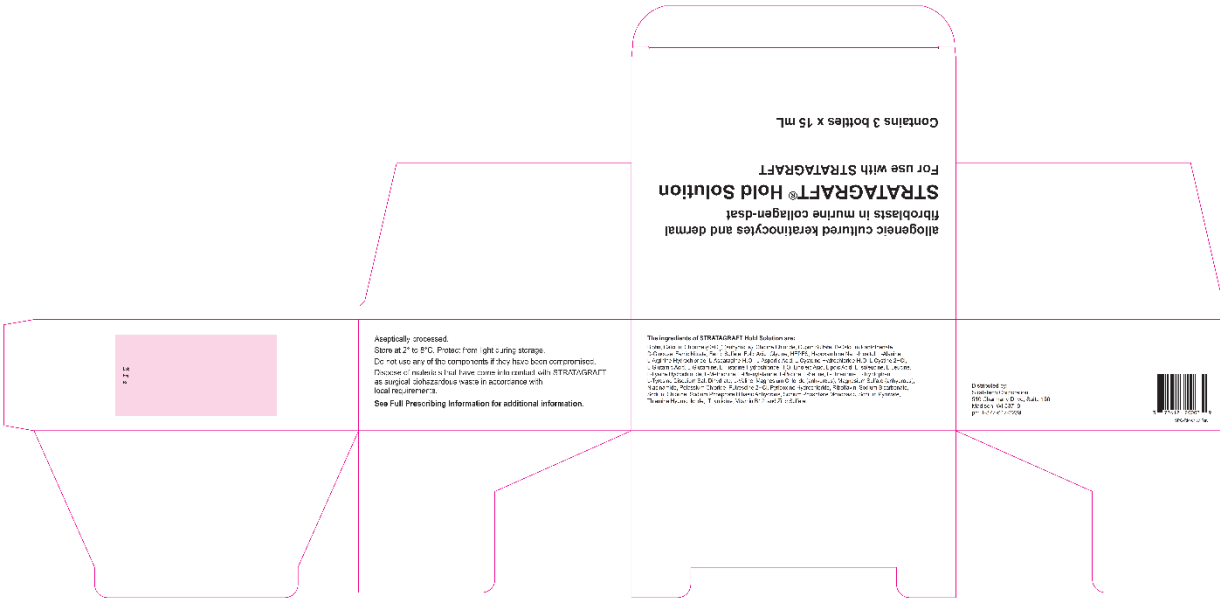
Hold Dish Tissue Carton Sticker Label: This is the label attached to each plastic, clear sealed bag that contains one Hold Dish



Hold Solution Pouch Label: This is the label on the foil pouch that contains each bottle of Hold Solution

Hold Solution Bottle Label: This is the label for each bottle of Hold Solution.

Hold Solution Carton Label: This is the label on each box that contains 3 bottles of Hold Solution



Hold Solution Carton Stick On Label: This is a stick-on label for the Hold Solution Carton

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Review Comment All labelling has been finalized.

Modules 4 and 5

Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

I reviewed Modules 4 and 5 to determine if there were elements requiring CMC input such as commentary on or validation of novel assays, or routine assessment of clinical and non-clinical testing. There were no such elements.

Overall Reviewer's Assessment of Relevant Sections of Module 4 and 5:

- There was no information regarding analytical or bioanalytical assessments for clinical or non-clinical studies that required CMC input.
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