fSummary Basis for Regulatory Action

Date:	**June 15, 2021**
From:	**Steven Bauer, PhD, Review Committee Chair, OTAT/DC**GT
BLA STN:	**125730**
Applicant:	**Stratatech Corporation**
Submission Receipt Date:	**June 5, 2021**
PDUFA Action Due Date:	**February 2, 2021**
Proper Name:	**allogeneic cultured keratinocytes and dermal fibroblasts in murine collagen-dsat**
Proprietary Name:	**STRATAGRAFT**
Indication:	**STRATAGRAFT 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).**

Recommended Action: The Review Committee recommends approval of this product.

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Director, Office of Tissues and Advanced Therapies

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Director, Office of Compliance and Biologics Quality

Document Reviews	Reviewer/Consultant – Office/Division
CMC • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Steven Bauer, PhD (OTAT/DCGT) Laura Ricles, PhD (OTAT/DCGT) Takele Argaw, DVM, MVSc (OTAT/DCGT) Terrig Thomas, PhD (OTAT/DCGT) Hector Carrero (OCBQ/DMPQ)
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Statistical • *Clinical data*	Stan Lin, PhD (OBE/DB)
Pharmacology/Toxicology • *Toxicology (product office)*	Abigail Shearin, VMD, PhD (OTAT/DCEPT)
Labeling • *Promotional (OCBQ/APLB)*	Michael Brony, PharmD (OCBQ/APLB)
Other Review(s) not captured above categories, for example • *Consult reviews*	Dan (Kelly) Wang, PhD (CBER/OTAT/DHT) Most Nahid Parvin, PhD (OCBQ/DBSQC) Simleen Kaur, MS (OCBQ/DBSQC)\ Varsha Garnepudi, MS (OCBQ/DBSQC) Berk Oktem, PhD (CDRH/OSEL/DBCMS) Tek Lamicchane, PhD (CDRH/OHT4/THT4B4) John Azeke, PhD (CDRH/OPEQ/OHTIV/DHTIVB)
Advisory Committee Summary	NA

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1. Introduction

Stratatech Corporation submitted a Biologics License Application (BLA), STN 125730, for licensure of allogeneic cultured keratinocytes and fibroblasts in murine collagen-dsat with the proprietary name STRATAGRAFT. STRATAGRAFT is indicated for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns).

STRATAGRAFT is a tissue-engineered epidermal allograft that contains a fully-stratified epithelial layer comprised of differentiated keratinocytes from a single human donor, layered over a dermal-like structure derived from a mixture of differentiated normal human fibroblasts from a different donor in a murine collagen type I scaffold. STRATAGRAFT is a xenotransplantation product because the keratinocyte cell-line component of STRATAGRAFT was originally derived in the presence of a mouse cell line.

Thermal burns containing intact dermal elements for which surgical intervention is clinically indicated, also known as deep partial-thickness (DPT) burns, involve the entire epidermis and approximately the top two-thirds of the dermis. Without autografting, a DPT wound requires more than 3 weeks to heal.

This document summarizes the basis for traditional approval of STRATAGRAFT. A Phase 3 clinical trial and a Phase 1 clinical trial provide substantial evidence of effectiveness and safety of STRATAGRAFT for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns). Data from two additional trials in subjects with full-thickness complex skin defects contribute further to the safety database. The recommendation for approval is based on the wound closure rate of STRATAGRAFT-treated sites, and significantly decreased need for autograft in STRATAGRAFT-treated sites, demonstrated in the Phase 3 and Phase 1 clinical trials. The more serious risks of STRATAGRAFT include potential hypersensitivity reactions to murine collagen or products containing ingredients of bovine or porcine origin, potential transmission of infectious disease agents, and potential dermal malignancy. None of these potentially serious risks were observed in subjects in clinical trials of 12-month duration. Common adverse reactions reported in the clinical trials (incidence ≥ 2%) include pruritus, blisters, hypertrophic scar and impaired healing.

The review team recommends regular approval of this BLA with the following Chemistry, Manufacturing, and Control (CMC) Postmarketing Requirement (PMR) and Postmarketing Commitments (PMCs):

- PMR: 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 Applicant is deficient in their viral inactivation/clearance study by only achieving a (b) (4) clearance for two of three model viruses (> 6 log 10 is FDA's current recommendation). For the third model virus (Murine Minute Virus), the reported data did not demonstrate clearance. Overall, this issue will not be considered sufficient to warrant a Complete Response 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/inactivation study as a Title IX PMR. This would demonstrate clearance or inactivation of model viruses Parainfluenza virus type 3 (PI3), Pseudorabies virus (PRV) and Murine Minute Virus (MMV). The Applicant would need to show a clearance level of >6 log 10 for all viruses.

- PMCs: The cell banks are characterized for appropriate adventitious virus testing, identity by genetic markers, and by functional assessments including viability, proliferation capacity, and ability to produce product that meets quality attributes. However, two additional characterization tests are needed and form the basis of two PMCs. The current (b) (4) identity testing is based on a method that will not detect contaminating cells, therefore, for the first PMC, the Applicant commits to implement a (b) (4) method that can confirm the identity of the NIKS and normal human dermal fibroblast (NHDF) cell banks and detect the presence of (b) (4)

(b) (4) . Cell bank characterization does not include validated measurements for unique cell identity or function. Therefore, for the second PMC, the Applicant commits to develop validated tests that would be stability-indicating and predictive of acceptable manufacturing capability.

2. Background

Disease Background

A thermal burn containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness [DPT] burn) is a serious condition because it causes skin loss, putting patients at significant risk for hospitalization, infection, and death. According to the American Burn Association (ABA) data, every year over 450,000 serious burn injuries occur in the United States that require medical treatment, resulting in approximately 40,000 hospitalizations. Approximately one third of patients requiring hospitalization for severe skin loss due to burn-related incidences require the surgical intervention of skin grafting.

Available Therapies

To achieve wound closure in a reasonable timeframe with acceptable functional and cosmetic outcomes, the standard of care for DPT thermal burn wounds is excision and autologous skin grafting (autografting). The autograft includes the epidermal layer which regenerates, and a very thin portion of the dermal layer which does not regenerate. In a larger total body surface area (TBSA) burn (usually > 30%), the donor skin has to be meshed and expanded in an attempt to cover a larger surface area with a smaller amount of available skin. Autografting is a surgical procedure involving the harvest of healthy skin from an uninjured site on the patient (the donor site) and its transplantation to the DPT thermal burn site. Autografting is effective at achieving durable wound closure in the majority of patients; however, it is associated with serious morbidity, such as pain, scarring, and susceptibility to infection at the donor site. Additionally, intact autologous skin tissue can be a limited resource in patients with more extensive DPT thermal burns.

RECELL Autologous Cell Harvesting Device (PMA #BP170122) and Epicel (HDE # BH990200) are two FDA-approved devices for the treatment of DPT burns. RECELL produces an autologous cell suspension while Epicel produces autologous sheets of keratinocytes. Thus, both products require presence of intact donor site(s) to provide the autologous sample for production of the cellular product. In addition, the safety and effectiveness of RECELL used alone (i.e., without meshed autograft) have not been established for treatment of partial-thickness burn wounds in patients with wounds totaling >20% TBSA. Epicel is a Humanitarian Device for use in patients with DPT burns comprising a TBSA of greater than or equal to 30%. It may be used in conjunction with split-thickness autografts, or alone in patients for whom split-thickness autografts may not be an option due to the severity and extent of their burns. The effectiveness of the device for this use has not been demonstrated.

There is an unmet medical need for the treatment of DPT thermal burns that reduce or eliminate the need for autografting or the need for autologous sampling.

Regulatory History
Key regulatory milestones in the development of STRATAGRAFT are summarized in Table 1.

Table 1 Regulatory Milestones

Date	Milestones
10/25/2001	Pre-IND meeting
11/7/2001	IND submission
5/6/2011	End-of-Phase 1 meeting
5/21/2012	Orphan Drug designation granted
6/16/2016	Pre-Phase 3 meeting
7/6/2017	RMAT designation granted
6/5/2020	BLA 125730 submission
7/31/2020	BLA filed, Priority Review
10/2/2020	BLA 120-day Safety and Efficacy Update received
2/2/2021	PDUFA* Action Due Date. 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.

*PDUFA=Prescription Drug User Fee Act

3. CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

a) Product Quality

The review team concludes that the STRATAGRAFT manufacturing process and controls can produce a product with consistent quality attributes, and the review team recommends approval.

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.

The product is supplied with a Hold Solution and a Hold Dish that allow for uniform and controlled product thawing and handling during preparation at the clinical site.

The product is made for topical application. The number of 100cm^2 constructs applied will vary, depending on the size of the wound bed.

Manufacturing Summary

STRATAGRAFT is manufactured in a continuous process encompassing (b) (4), from initiation of cell culture ((b) (4)), to formation of a dermal equivalent consisting of NHDF cells mixed with rat-tail collagen type I ((b) (4)), to seeding of NIKS keratinocytes cells over the dermal equivalent ((b) (4)), to maturation and development of a bilayered skin-like tissue construct in a custom tissue culture apparatus ((b) (4)), to final packaging and cryopreservation in a novel tissue tray sealed in a foil package ((b) (4)). The product has a twelve-month shelf-life under cryopreservation at -80°C. Each of the packaged constructs is a single unit, and the process is validated to manufacture at a (b) (4) scale.

Manufacturing Controls

The manufacturing control strategy begins with a raw material and reagent qualification program consisting of source material risk assessment, vendor qualification, and confirmation of certificate of analysis and material testing.

Manufacturing control strategies also include testing and characterization of the NHDF and NIKS master cell banks (MCBs) and working cell banks (WCBs), process performance qualification (PPQ) studies, and appropriate in-process testing ((b) (4)) for the phases of manufacturing. The phases include: (b) (4) final cryopreservation of the construct; and 7) 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). 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 of acceptable quality. These conclusions support approval of the BLA.

Process Validation

The commercial STRATAGRAFT manufacturing process was assessed at the Stratatech Corporation facility in Madison, Wisconsin by performing manufacturing at

the (b) (4) scale. The process validation was assessed against established key operating process parameters and predefined release criteria. The manufacturing process validation demonstrated removal of process-related impurities, including (b) (4) used during all stages of manufacturing. Shipping was validated for all shipping steps. Additional validation studies included aseptic process simulations, studies to determine the stipulated STRATAGRAFT thaw temperature and time, studies to determine the stipulated Hold Solution (b) (4), and studies to determine the stipulated conditions for STRATAGRAFT (b) (4) hold solution temperature and holding time.

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

The final lot release specifications are shown in Table 2.

Table 2. STRATAGRAFT lot release specifications

Test	Acceptance Criteria
Appearance	Skin tissue should be translucent and off-white in color; majority of skin tissue surface should be covered by and epidermal layer; minor irregularities such as wrinkling, contraction, and variation in skin tissue thickness and/or opacity are acceptable.
Histology	(b) (4)
Viability	(b) (4)
Barrier Function	(b) (4)
(b) (4)	(b) (4)
Sterility	No growth
Endotoxin	(b) (4)
Mycoplasma	Not detected

Container Closure
The container closure system for the drug product includes the product dish, insert/membrane and pouch. The primary packaging components used for STRATAGRAFT are described in Table 3. 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. Stratatech conducted the container closure integrity testing (CCIT) employing the (b) (4) method; all acceptance criteria were met.

Table 3. Primary packaging

Components		
Product Dish	Vendor	(b) (4)
	Resin Vendor	(b) (4)
	Description	(b) (4) Rectangular Tray
	Material	(b) (4)
	Sterilization Technique	(b) (4)
Insert/Membrane	Vendor – tissue insert	(b) (4)
	Vendor – tissue membrane	(b) (4)
	Description	100cm2 Rectangular Insert
	Material	(b) (4)
	Sterilization Technique	(b) (4)
Pouch	Vendor	(b) (4)
	Description	48ga PET, White LDPE, 0.35mil aluminum foil, LDPE, 2.0 mil Sealant Layer
	Material	(b) (4)
	Sterilization Technique	(b) (4)

The container closure system for the Hold solution, considered an excipient, consists of a 20 mL PETG bottle ((b) (4)) and HDPE cap ((b) (4)) containing a HDPE/LDPE liner ((b) (4)). The Hold Solution bottles are neck-wrapped and pouched in a (b) (4) pouch consisting of nylon and aluminum foil laminate with an ethylene vinyl acetate copolymer seal. The Hold Dish is an identical component to the STRATAGRAFT Product Dish, the primary closure for the STRATAGRAFT. Each Hold Dish is individually pouched for shipment to clinics. Stratatech conducted the CCIT of the bottles using a (b) (4) method; all acceptance criteria were met.

Stability

Long-term stability studies support 12 months of storage for STRATAGRAFT when stored at or below -80°C. The STRATAGRAFT stability studies used development ((b) (4) scale) and commercial ((b) (4) scale) batches. The Hold Solution is stable for 12 months when stored at 2-8°C. Results from stress studies demonstrate that both viability and potency ((b) (4)) are stability-indicating attributes and are significantly changed at stressed conditions. In-use stability testing supports a post-thaw expiry of 4 hours. An acceptable post-approval long-term stability protocol is provided for both STRATAGRAFT and the Hold Solution.

b) CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. Failure of a single lot will have minimal potential impact on public health.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of STRATAGRAFT are listed in the table below. The activities performed and inspectional histories are noted in Table 4.

Table 4. Facilities

Name/Address	FEI Number	DUNS Number	Inspection/Waiver	Justification/Results
Drug Substance and Drug Product Manufacturing, Release testing, Packaging, Labeling Stratatech Corporation 535 Science Drive Madison, WI 53719	3009105377	117110703	Pre-License Inspection	CBER/DMPQ May 3-7, 2021 NAI
Release Testing (b) (4)	(b) (4)	(b) (4)	Waiver	ORA (b) (4) Surveillance NAI

Name/Address	FEI Number	DUNS Number	Inspection/Waiver	Justification/Results
Release Testing (b) (4)	(b) (4)	(b) (4)	Waiver	ORA (b) (4) Surveillance NAI

CBER conducted a pre-license inspection (PLI) at Stratatech Corp. in May 3 - 7, 2021. No Form FDA 483 was issued at the end of the inspection and the inspection was classified as No Action Indicated (NAI).

ORA conducted a surveillance inspection of the (b) (4) facility in (b) (4). No Form FDA 483 was issued and the inspection was classified as No Action Indicated (NAI).

ORA performed a surveillance inspection of the (b) (4) facility in (b) (4). No Form FDA 483 was issued and the inspection was classified as No Action Indicated (NAI).

d) Environmental Assessment

A request for categorical exclusion from an Environmental Assessment per 21 CFR 25.31(c) was provided in the BLA. This request and supporting information provided by Stratatech Corporation is acceptable to conclude that STRATAGRAFT poses a negligible risk to the environment or to the general public. There are no significant environmental or public health impacts posed by the product or its manufacturing. Categorical exclusion under 21 CFR 25.31(c) is therefore acceptable.

e) Product Comparability

Studies to demonstrate comparability of products manufactured using processes version 1, 2, 3, 4, and 5 were performed under IND10113. These studies included comparability using two different product formats ((b) (4) cm^2 and 100 cm^2) and product manufactured at scales of (b) (4) per lot. These studies demonstrated that STRATAGRAFT products manufactured with each process were comparable. No future manufacturing changes to be evaluated under a comparability protocol were proposed in the BLA.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

In vitro studies showed that NIKS keratinocytes and human dermal fibroblasts cultured for (b) (4), respectively, are karyotypically stable, consistent with a Master Cell Bank for each cell line. NIKS keratinocytes and human dermal fibroblasts cultured for 43 and 6 passages, respectively, did not exhibit anchorage-independent growth (a standard assay that evaluates the potential for cellular transformation). Of note, the commercial STRATAGRAFT product contains NIKS keratinocytes and human dermal fibroblasts that are at passage 40 and 7, respectively.

In vivo evaluation of STRATAGRAFT included assessment of safety, tolerability, and tumorigenic potential following topical administration on full-thickness excisional wounds that were greater than 25% of the total body surface area of immunodeficient mice. No tumor formation was observed for the 20-week study duration. In addition, following a single subcutaneous injection of NIKS keratinocytes in immunodeficient mice, no tumor formation was detected for the 23-week study duration.

No animal reproductive or developmental toxicity (DART) studies were conducted with STRATAGRAFT, which is acceptable, considering the product characteristics and safety profile.

5. CLINICAL PHARMACOLOGY

STRATAGRAFT contains metabolically active cells that produce and secrete a variety of growth factors and cytokines. *In vitro* studies have shown that STRATAGRAFT secretes human growth factors and cytokines and contains human extracellular matrix proteins. Growth factors, cytokines, and extracellular matrix proteins are known to be involved in wound repair and regeneration. 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. A total of 85 subjects in the Phase 1 and Phase 3 clinical trials were evaluated at 3 months for persistence of allogeneic STRATAGRAFT DNA at the treatment site. STRATAGRAFT-associated DNA was not detected in these subjects.

The pharmacodynamic and pharmacokinetic effects of STRATAGRAFT are not known.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The Phase 3 trial and the Phase 1 trial form the basis of the review team's recommendation for regular approval of STRATAGRAFT for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns). The Phase 3 trial provides the primary evidence of effectiveness, and results of the Phase 1 trial provide supportive evidence of effectiveness.

The Phase 1 and Phase 3 trials, as well as two trials in subjects with full-thickness complex skin defects, contribute to the safety database.

Study Description
The Phase 3 trial is an open-label, intra-subject autograft-controlled, randomized study. The study was designed to evaluate the efficacy and safety of STRATAGRAFT in adults with acute thermal burns containing dermal elements for which excision and autografts were clinically indicated (deep partial-thickness burns).

The Phase 1 trial is an open-label, intra-subject-controlled, randomized, dose-escalation study in adults with deep partial-thickness burns. It was designed to evaluate safety and preliminary efficacy.

In both trials, following surgical removal of nonviable tissues, two deep partial-thickness (DPT) burn wounds of comparable area and depth on each subject were identified and randomized to receive either a single topical application of STRATAGRAFT or autograft. In addition, two areas of healthy skin of each subject were identified as donor sites and designated to provide a source of autograft for the autograft treatment site and, if needed, for the STRATAGRAFT treatment site. An autologous skin graft was surgically harvested from one of the donor sites and was meshed with a mesh to skin ratio up to 4:1, per standard of care (SOC), and secured in place at the autograft treatment site using staples, sutures, or tissue adhesive. For STRATAGRAFT treatment sites, the STRATAGRAFT construct was meshed 1:1, trimmed to fit the wound as necessary, and secured in place using staples, sutures, or tissue adhesive. Duration of follow-up was 12 months for both trials.

Efficacy Endpoints
The two primary efficacy endpoints in the Phase 3 trial were:

a. The percent area of study treatment sites and the control autograft treatment site that requiring autografting by 3 months after STRATAGRAFT or autografting.

b. The proportion of subjects achieving durable wound closure of the STRATAGRAFT treatment site at 3 months without autograft placement.

The second primary efficacy endpoint of durable wound closure at 3 months without autograft placement was deemed successful if the lower bound of the 95% confidence interval (CI) was ≥ 50% among all the STRATAGRAFT treatment sites. Durable wound closure at 3 months was defined as wound closure at two consecutive study visits at least 2 weeks but no more than 5 months apart and including or encompassing the time point of 3 months. Wound closure of the treatment site was defined as complete skin re-epithelialization and the absence of drainage.

The two primary efficacy endpoints in the Phase 1 trial were:

a. The percent area of STRATAGRAFT treatment site requiring autograft by 28 days after STRATAGRAFT treatment

b. The proportion of treatment sites that achieved complete wound closure by 3 months.

Complete wound closure was defined as ≥95% re-epithelialization in the absence of drainage.

Clinical Efficacy Findings

Phase 3 Clinical Trial

The study enrolled 71 adults with acute DPT thermal burns involving 3 to 37% total body surface area (TBSA). The time from burn to study treatment was 1 to 18 days. The range of the STRATAGRAFT-treated wound area in STRATA2016 was 12 to 960 cm^2. The mean age was 44 years (19 to 79 years).

Among the 71 STRATAGRAFT-treated sites, three required autografting to achieve wound closure. Among the 71 autograft-treated sites, two required repeated autografting to achieve wound closure. Therefore, 4.3% (3/71) of the STRATAGRAFT treatment sites and 102.1% (73/71) of the autograft treatment sites were autografted by 3 months. The difference in the percent area of STRATAGRAFT and control autograft treatment sites that required autografting by 3 months was 97.8% ± 16.6% ($p<0.0001$). Donor site harvest was eliminated in 96% of STRATAGRAFT-treated DPT burns**.**
The proportion of subjects achieving durable closure of the STRATAGRAFT treatment site at 3 months without autograft placement was 83.1% (95% CI: 74.4, 91.8). The lower bound of the 95% CI was above the pre-defined null threshold of 50%. The proportion of subjects achieving durable closure of the autograft control treatment site at 3 months without additional autograft placement was 86% (95% CI: 77.8, 94.0).

Phase 1 Clinical Trial

The study enrolled 30 adults with DPT thermal burns involving 3 to 49% TBSA. The time from burn to study treatment ranged from 3 to 13 days. The size of the STRATAGRAFT-treated wound was 52 to 440 cm^2. The mean age was 41 years (21 to 63 years).

No STRATAGRAFT treatment site required autografting by 28 days. Between 28 days and 3 months, one subject had both the STRATAGRAFT treatment site and the autograft site treated with autografts, and a second subject had 25% of the STRATAGRAFT treatment site autografted. At 3 months, 93.1% of STRATAGRAFT treatment sites and 100% of autograft treatment sites achieved complete wound closure. All STRATAGRAFT treatment sites remained closed when evaluated at 6 months and 12 months after treatment.

Efficacy Conclusion

The submitted data from one adequate and well-controlled Phase 3 trial and one confirmatory Phase 1 trial provide substantial evidence of effectiveness for the

treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns). This conclusion is based on the percentage of STRATAGRAFT treatment sites that achieved durable complete wound closure, and significantly decreased need for autografts at the STRATAGRAFT treatment sites.

Bioresearch Monitoring
Bioresearch Monitoring (BIMO) inspections were conducted for the Applicant of this original BLA and five clinical study sites that participated in the conduct of studies, STRATA 2011 or STRATA 2016. The inspections did not reveal substantive issues that impact the data submitted in the BLA.

b) Pediatrics

Pediatric Research Equity Act (PREA) is not applicable to STRATAGRAFT for the treatment of thermal burns containing intact dermal elements for which surgical intervention is clinically indicated because STRATAGRAFT was granted orphan drug designation for the indication.

Only adult subjects were enrolled in STRATAGRAFT clinical trials.

c) Other Special Populations

None.

7. SAFETY

The safety population comprised 119 adults treated with STRATAGRAFT in four clinical trials conducted in the United States. Among the 119 subjects, 101 subjects with DPT thermal burn received STRATAGRAFT topically in the Phase 3 and Phase 1 trials, and 18 subjects with full-thickness complex skin defects received STRATAGRAFT topically in two other trials. Each subject received topical application of STRATAGRAFT at one wound site and either autografting (104 subjects) or cadaver allografts (15 subjects) at the other wound site that serves as the intra-subject control. The study populations ranged in age from 19 to 79 years (mean age 43 years).

There were two deaths in the Phase 3 trial. The cause of death in one subject was acute myocardial infarction. The cause of death in the other subject was acute myocardial infarction, cardiac arrest, and sepsis. Neither death is considered by FDA to be related to STRATAGRAFT.

The most frequently reported adverse reactions (incidence ≥ 2%) observed in the 4 trials were pruritus (11%), blister (4%), hypertrophic scar (3%), and impaired healing (3%). No subjects discontinued study participation due to adverse reactions. Overall, the safety profile of STRATAGRAFT with regard to wound-related events, including erythema, swelling, local warmth and wound site infections, and was similar to what was

observed at the autograft sites in these trials. There were no reports of rejection of STRATAGRAFT. The safety of STRATAGRAFT beyond 12 months was not evaluated in the clinical trials.

STRATAGRAFT contains cells from human donors and is a xenotransplantation product. Therefore, STRATAGRAFT carries the potential risk of transmitting infectious diseases or infectious agents. STRATAGRAFT may cause hypersensitivity reactions to murine collagen or products containing ingredients of bovine or porcine origin, because STRATAGRAFT product manufacture includes reagents derived from animal materials, including rat-tail collagen, calf serum, porcine trypsin and purified bovine serum albumin. The layer of NIKS human keratinocytes in STRATAGRAFT have a known and well-characterized chromosomal abnormality that is karyotypically stable during manufacture. *In vivo* evaluation of NIKS keratinocytes in mice demonstrated no tumor formation. There was no persistence of cells of STRATAGRAFT in treated subjects and there have been no documented clinical or histological reports of tumor formation at the STRATAGRAFT application sites. At 3 months, STRATAGRAFT-associated DNA was not detected in the 85 subjects evaluated for persistence of allogeneic STRATAGRAFT DNA at treatment sites. Although the risk of dermal malignancy after use of STRATAGRAFT is thought to be low, this remains a potential risk. None of these potential risks were observed in subjects in clinical trials of 12 months duration.

In summary, the potential serious risks associated with topical application of STRATAGRAFT include hypersensitivity reactions to murine collagen or products containing ingredients of bovine or porcine origin, transmission of infectious diseases or agents, and dermal malignancy. None of these potential risks were observed in subjects in clinical trials of 12-month duration. The most common adverse reactions include pruritus, blister, hypertrophic scar, and impaired healing. These risks can be mitigated by routine medical management, appropriate labeling of Prescribing Information (PI), and the postmarketing pharmacovigilance plan proposed by the Applicant.

Postmarketing Pharmacovigilance

The Applicant will conduct the following pharmacovigilance activities for postmarketing safety monitoring for STRATAGRAFT:

a. Routine pharmacovigilance and adverse event reporting in accordance with 21 CFR 600.80,

b. Enhanced pharmacovigilance and submission of expedited 15-day reports for dermatological malignancy(ies), unexpected infections, and clinical events that are suspicious of a xenogeneic cause,

c. A summary of relevant data from the STRATAGRAFT patient and product information database in periodic safety reports at quarterly intervals for 3 years post-licensure and annual intervals thereafter.

The safety data do not indicate the need for a Risk Evaluation and Mitigation Strategy (REMS) or clinical safety PMR. The review team recommends regular approval of this BLA with the CMC safety PMR on collagen viral clearance/inactivation.

8. ADVISORY COMMITTEE MEETING

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

9. OTHER RELEVANT REGULATORY ISSUES

STRATAGRAFT xenotransplantation product designation plan, in accordance with the FDA *Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans* (2016), was communicated with the Applicant via Exemption Request Denial Letter, dated December 18, 2020.

10. LABELING

The proposed proprietary name, STRATAGRAFT, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on July 8, 2020, and was found acceptable. CBER communicated the acceptability of the proprietary name to the Applicant on July 15, 2020.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information, package labeling, and the container Label on November 9, 2020 and found them acceptable from a promotional and comprehension perspective.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

Based on the treatment effect demonstrated in the Phase 3 trial and supported by the Phase 1 trial, the review team recommends traditional approval for STRATAGRAFT.

b) Risk/ Benefit Assessment

Efficacy of STRATAGRAFT is based on 97.8% reduction in the need of autografting at STRATAGRAFT-treated DPT burn sites. Without additional autografting, 83.1% of STRATAGRAFT-treated sites achieved durable wound closure at 3 months, compared with 86% of autograft-treated sites.

The more frequently reported adverse reactions were pruritus, blister, hypertrophic scar, and impaired healing. The potential serious risks associated with topical application of STRATAGRAFT include hypersensitivity reactions to murine collagen or products

containing ingredients of bovine or porcine origin, transmission of infectious disease agents and dermal malignancy. In clinical studies, dermal malignancy and transmission of infectious disease agents by STRATAGRAFT did not occur. These risks can be mitigated by the enhanced pharmacovigilance plan, adequate Prescribing Information (PI), and additional postmarketing measures associated with the xenotransplantation nature of STRATAGRAFT. The potential unexpected serious risk of exposure to murine viruses such as murine parvovirus will be addressed by the CMC safety-related PMR requiring viral clearance studies.

Thus, STRATAGRAFT provides the benefit of wound closure while addressing the unmet need by largely avoiding the morbidity (particularly pain) associated with autografting and autologous sampling, and the risks of STRATAGRAFT are either relatively minor or can be appropriately mitigated. Therefore, the efficacy and safety data in the BLA support a favorable benefit-risk profile of STRATAGRAFT for the treatment of adults with thermal burns containing intact dermal elements for which surgical intervention is clinically indicated (deep partial-thickness burns). The review team recommends traditional approval of STRATAGRAFT with a recommended one-time application to a surgically prepared wound bed. The number of STRATAGRAFT constructs applied will vary depending on the size of the wound bed. STRATAGRAFT constructs may be trimmed to accommodate the size and shape of the wound bed. Each STRATAGRAFT construct is for application to a single patient only.

c) Recommendation for Postmarketing Activities

The Applicant agreed to the following CMC PMR.

PMR #1: 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.

The timetable for the PMR study on collagen viral clearance is:
Draft protocol to FDA: September 30, 2021
Final protocol to FDA: November 30, 2021
Study completion: March 31, 2022
Final report: April 30, 2022

The Applicant agreed to the following CMC PMCs:

PMC #2:

Stratatech commits to implement a (b) (4) 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 #3:

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 ongoing stability studies.

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

The review team agrees with the postmarketing risk mitigation plans proposed by the Applicant, including adequate information provided in the PI and patient information sheet, enhanced pharmacovigilance plan, and additional measures associated with xenotransplantation nature of STRATAGRAFT.

The pharmacovigilance plan includes routine pharmacovigilance for adverse event reporting and enhanced pharmacovigilance for expedited reporting of dermatological malignancy(ies), unexpected infection and any clinical events that are suspicious of a xenogeneic cause. The 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 will contain a summary of information from the database of patients treated with STRATAGRAFT.