Summary Basis for Regulatory Action

Date: March 9, 2012

From: Mark H. Lee, Ph.D., Chair of the Review Committee

BLA/ STN#: 125400/0

Applicant Name: Organogenesis Inc.

Date of Submission: May 13, 2011

PDUFA Goal Date: March 12, 2012

Proprietary Name: Gintuit

Proper Name: Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen

Indication: For topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. Gintuit is not intended to provide root coverage.

Recommended Action: Approval

Offices' Signatory Authorities:

Celia Witten, PhD, MD, Office Director, OCTGT

X I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Mary Malarkey, Director, Office of Compliance and Biologics Quality

X I concur with the summary review.
□ I concur with the summary review and include a separate review to add further analysis.
□ I do not concur with the summary review and include a separate review.

Material Reviewed / Consulted/Specific Documentation Used in Developing the SBRA

CMC Review	08-Mar-2012 Mark H. Lee, Eric Dollins, Charles Durfor
Clinical Review	08-Mar-2012 Agnes Lim, Robert Betz, Bruce Schneider, Susan Runner
Statistical Review	03-Feb-2012 John Scott
Nonclinical Pharmacology / Toxicology Review	28-Feb-2012 Patrick Au
Facilities Review	05-Mar-2011 Qiao Bobo, Gang Wang
Pharmacovigilance Review	09-Nov-2011 Faith Barash
Bioresearch Monitoring Review	08-Dec-2011 Janet White
Advertising and Promotional Labeling Review	28-Feb-2012 Loan Nguyen
Advisory Committee Transcript	16-Dec-2011
Establishment Inspection	07-Oct-2011 Qiao Bobo, Gang Wang
CBER Lot Release	01-Mar-2012 Karen Campbell
Environmental Assessment	05-Mar-2012 Qiao Bobo

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1. Introduction

Biologics License Application (BLA) 125400 is for Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen, Gintuit, which is manufactured by Organogenesis Inc. Gintuit is an allogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. Gintuit is not intended to provide root coverage.

Gintuit consists of two layers: an upper cornified layer that is made of human keratinocytes and a lower layer constructed of bovine-derived collagen, human extracellular matrix proteins, and human dermal fibroblasts. These components interact and produce the final bi-layered structure. The cells are isolated from donated human newborn foreskin tissue and are multiplied into cell banks used in large-scale manufacturing. The cell banks are tested for microbiological and cytogenetic safety.

The mechanism of action by which Gintuit increases keratinized tissue at the treated site has not been identified. *In vitro* studies have shown that Gintuit secretes human growth factors and cytokines, and contains extracellular matrix proteins. Growth factors, cytokines, and extracellular matrix proteins are known to be involved in wound repair and regeneration.

This document summarizes the basis for approval for Gintuit, highlighting topics of key review discussions. The review team recommends approval of this BLA with one postmarketing requirement (PMR) for a pediatric clinical study and five postmarketing commitments (PMC) related to CMC issues.

2. Background

Mucogingival Conditions

Mucogingival conditions are soft tissue defects that disrupt the normal anatomic relationship between the gingival margin and the mucogingival junction. These defects may be caused by anatomic, traumatic, or chronic inflammatory conditions. Chronic inflammation may predispose to progressive loss of gingival attachment, resulting in gingival recession and root exposure. Surgical intervention is warranted when the inflammation or gingival attachment loss can no longer be controlled with conservative oral hygiene measures. The main objective of periodontal mucogingival surgical procedures is to reduce the risk of gingival attachment loss; improvements in aesthetics may also result.

Soft tissue autografts, such as free gingival grafts (FGG), are widely used for the treatment of mucogingival conditions. These procedures create a vascular wound bed

that heals with soft tissue keratinization, thereby increasing the zone of keratinized gingiva around teeth. Gintuit is proposed for application to a surgically created vascular wound bed in the treatment of mucogingival conditions, such as the ones described above. Thus, Gintuit is proposed as an alternative to a FGG in the surgical treatment of mucogingival conditions.

Regulatory History and Considerations

The product used in clinical studies submitted to the BLA was manufactured in the same way as Apligraf, which is currently approved under a PMA. Apligraf was approved by FDA for the treatment of Venous Leg Ulcers (VLU) on May 22, 1998 and for the treatment of Diabetic Foot Ulcers (DFU) that have not healed with conventional therapies on June 20, 2000. While the regulatory experience of the approved PMA was considered, this application was reviewed according to the regulatory requirements for a BLA.

Throughout this document, the name "Apligraf" is used to denote the approved PMA product, and the name "Gintuit" is used for the product which is the subject of this BLA application. Organogenesis Inc. called the product "CelTx" during the clinical studies.

Three IDE studies for oral indications were completed prior to submission of BLA 125400 on May 13, 2011:

- G050122 – 05-PER-001: "A Pilot trial of Apligraf in establishing a functional zone of attached gingiva"
- G070012 – 06-PER-002: "A clinical trial to evaluate CelTx (Apligraf) as an alternative to tissue from the palate to enhance oral soft tissue regeneration and wound healing"
- G070178 – 07-PER-004-CTX: "A prospective, randomized, controlled pilot study of CelTx (Apligraf) as an alternative to tissue from the palate in the treatment of gingival recession requiring root coverage"

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Manufacturing Summary and Issues

Gintuit is manufactured by combining viable allogeneic human fibroblasts and keratinocytes with a type I bovine collagen biomaterial.

The allogeneic fibroblasts and keratinocytes are derived from human neonatal foreskin tissue. The fibroblasts and keratinocytes are expanded in culture separately to generate master and working cell banks (MCB, WCB) that are cryopreserved, and cells from the WCB are thawed when needed for manufacture of a lot of Gintuit. The heterogeneous

population of primary cells resulting from tissue dissociation is directed to produce a more homogeneous culture of keratinocytes and/or fibroblasts by means of cell selective and growth promoting media. Because expansion of the cell bank is limited, new banks from new donor tissue must be generated on a periodic basis.
The type I bovine collagen biomaterial is obtained by processing of –b(4)---------- by the Applicant. The processing includes steps for ---b(4)----------, and the resulting collagen is tested further for microbiological safety and physicochemical quality prior to use in manufacture.

The manufacturing process is 3-4 weeks duration. The critical production steps are described below.

- *Production of Dermal Equivalent (DE)*
  An acellular matrix layer of bovine collagen is ----b(4)----------. Fibroblasts are seeded onto this layer and grown for 6 days to create a dermal layer referred to as a dermal equivalent (DE).
- *Production of Epidermal Layer (EPI)*
  Keratinocytes are seeded onto the DE and incubated for 2 days.
- *Differentiation*
  The construct is incubated further under differentiating conditions.
- *Cornification*
  The construct is placed on supports at this stage to lift the upper surface of the developing construct out of the cornification medium ("Air Lift"). This condition is maintained for 9 days in total, with media exchanges until a differentiated, cornified (i.e., mature) product results.

The mature cell-scaffold product contains upper EPI and lower DE layers combined to form a bi-layered unit and make up approximately –b(4)------- of the construct, respectively. This construct is stored under conditions to maintain product quality ("Maintenance") until it can be packaged and shipped to the clinical site within a 15-day window.

Control Strategy

Safety and quality testing for Gintuit is comprised of three tiers: 1) donor testing and screening per requirements for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) outlined in 21 CFR 1271; 2) a panel of tests on the individual fibroblast and keratinocyte cell banks, including microbiological safety, adventitious viral safety, cytogenetic stability, tumorigenicity, purity, cell functionality and comparability; and 3) in-process and lot release tests per requirements of 21 CFR 610, including sterility, mycoplasma, endotoxin, identity, and potency.

Cell Bank Testing

Qualification of cell banks includes several broad test categories: adventitious agent testing, neoplastic safety testing, *in vitro* and *in vivo* comparability testing, identity testing, and cell performance characterization. The number of cells obtained from the primary tissue is limited, resulting in a relatively small MCB. There are also a low number of passages between the MCB and creation of the WCB. Therefore, the testing scheme for qualification of the MCB and WCB is designed with overlap. To obtain sufficient cells for MCB testing, a portion of the MCB is passaged using the same conditions used to generate the WCB. The overall testing scheme includes tests that are performed on cells from this MCB passage (referred to as Master Cell Bank Test Cells (MCBTC), cells from the WCB, and on final cell-scaffold constructs made from MCB and WCB cells.

MCB qualification testing includes microbiological and viral safety testing, neoplastic safety testing (isoenzyme analysis, karyology, senescence determination, tumorigenicity testing), *in vitro* comparability (cell purity, percutaneous absorption, cytokine profile assay, Mitochondrial Tetrazolium Test (MTT), histology, VEGF quantitation, and *in vivo* comparability in nude mice (histology, involucrin expression, graft take, integration and contraction)). WCB qualification testing includes microbiological and viral safety testing, identity (isoenzyme analysis, collagen biosynthesis for fibroblasts, involucrin for keratinocytes), cell performance (cell growth, viability), and *in vitro* comparability (histology).

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

Cell Bank Review Issues

- Karyotypic stability of the culture-expanded fibroblasts and keratinocytes was identified as a potential safety concern. The testing results for cytogenetic analysis of all MCBs generated since 2000 were submitted to the BLA and the data showed a consistently low frequency of chromosomal aberrations. These data are sufficient to address safety concerns related to karyotypic stability.

- The Advisory Committee noted that each Gintuit lot can be composed of different donor pairings between keratinocyte and fibroblast cell strains and that more quantitative biological data were needed to support equivalent activity of product lots manufactured with different pairs of fibroblast and keratinocyte banks. The Applicant has provided a summary of historical results obtained from the

combination of keratinocyte cell strains paired with unmatched fibroblast cell strains that have been approved by FDA (CDRH) for commercial production since 1997. Analysis of these data suggests there is no substantive difference among the cell banks.

- The fibroblasts and keratinocytes used to generate lots of the product are not typically from the same donor. An exemption to donor pooling prohibition per 21 CFR 1271.220(b) was requested and has been granted by CBER.

Product Lot Release and In-Process Testing

The safety and quality of Gintuit is ensured by the testing strategy shown in Table 1. It is noted that lot release is required prior to the full evaluation of product sterility due to the limited shelf-life.

Table 1. Product In-Process and Lot Release Testing

[b(4)]

Product Testing Review Issues

- The use of the histology assay to measure product potency, as proposed by the Applicant, was discussed by the Advisory Committee. The Committee noted that the histology assay is a good measure of the structural integrity of the product, however, the assay is not an adequate, sensitive measure of biological activity. While the exact biological metric that is most appropriate for product potency remains unclear, the Committee discussed that it would be appropriate to include cytokine assays given the current understanding of product function.

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

- Visual inspection testing was modified to act as a true lot release assay, with appropriate acceptance criteria supported by statistical analyses of data from manufactured lots.

Comparability Assessment

The product used in the three investigational device exemption studies for the oral indication was manufactured at the –b(4)------scale for the approved device Apligraf, in the manufacturing site in Canton, Massachusetts.

Manufacturing Risks, Potential Safety Concerns and Management

The risks from the manufacturing process for Gintuit involve two main areas: 1) the risk of product contamination from operators during an extensive, manual aseptic manufacturing process; and 2) the risk of microbiological or viral contaminants from critical raw materials, including those from human and animal sources.

Regarding the first issue, the review team assessed the manufacturing history of Apligraf as well as Gintuit during the investigational studies. The team's assessments were based on review of documents submitted to the BLA and the direct observation of manufacturing processes and quality systems assessment during pre-license inspection (PLI) of the Canton, MA facility (see below *Facilities review/inspection*).

Regarding the second issue, the review team assessed the sourcing and testing information for all raw materials that are of human and animal origin. The critical reagents included the cellular materials (keratinocytes and fibroblasts), bovine collagen, bovine pituitary extract (BPE), ----b(4)----------, collagenase, ---b(4)----------. All necessary information to address potential microbiological and adventitious viral contaminants in these critical reagents was requested and reviewed during the BLA review cycle. All issues have been resolved.

However, despite controls on sourcing of bovine materials to minimize the risk of the presence of the infectious agent of bovine spongiform encephalopathy (BSE), the theoretical risk cannot be dismissed. A statement regarding this risk has been included in the Warnings section of the Prescribing Information. ----b(4)---- ----------
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b) CBER Lot Release

Gintuit will be exempt from CBER Lot Release including no requirement for submission of lot release protocols or product samples to CBER for the following reasons.

- Safety testing is performed as part of donor testing and screening per requirements for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) outlined in 21 CFR 1271.
- A panel of tests for safety and quality are performed on the individual fibroblast and keratinocyte cell banks, including microbiological safety, adventitious viral safety, cytogenetic stability, tumorigenicity, purity, cell functionality and comparability.
- In-process and lot release tests per requirements of 21 CFR 610, including sterility, mycoplasma, endotoxin, identity, and potency are performed.
- Gintuit undergoes a continuous process from manufacture to clinical application and possesses a limited shelf-life (15 days) once released for packaging/shipping. CBER lot release including protocol review and confirmatory testing would exceed the time window in which the product is requested by the clinician and available to be applied to the patient.

c) Facilities review/inspection

A pre-license inspection (PLI) of Organogenesis Inc. in Canton, MA for manufacturing of Gintuit under Biologics License Application STN 125400/0 (License No. 1863; FEI: 1000148471) was conducted from October 3-7, 2011. This facility is the only manufacturing site for Gintuit and Apligraf.

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FEI Number: 1000148471

Organogenesis had been previously inspected under compliance program 7382.845 – Inspection of Medical Device Manufacturer (QSIT Level 2 comprehensive inspection) by FDA's field investigators with no major issues. The PLI in October 2011 by members of CBER/DMPQ and CBER/OCTGT revealed objectionable conditions regarding aseptic processing techniques, environmental monitoring, in-process testing criteria, process validation, sample retention, equipment maintenance and calibrations, and sterility testing. A 9-item Form FDA 483, List of Inspectional Observations, was issued regarding these and other observations. The firm provided a formal response to the 483 items on

December 29, 2011 and in subsequent amendments, and all items have been adequately addressed.

Based on the 2011 inspection, the overall compliance status of Organogenesis's Canton, MA manufacturing facility is deemed acceptable for product approval.

The team recommends a postmarketing commitment to submit the ----b(4)---- ----------
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d) Environmental Assessment

Organogenesis Inc. requested categorical exclusion from an environmental assessment pursuant to 21 CFR 25.31(c), which applies to a biologic product containing substances that occur naturally in the environment when the introduction of the product does not alter significantly the concentration or distribution of the substances, their metabolites, or degradation products in the environment. The request for categorical exclusion is justified as the product meets the applicable exclusion criteria in 21 CFR Part 25, and there is no information indicating that extraordinary circumstances exist.

4. Nonclinical Pharmacology / Toxicology

In addition to the nonclinical studies submitted to the Apligraf PMA, two nonclinical studies were also submitted to this BLA.

In nonclinical pharmacology studies for the cutaneous wound indication, the data suggest that Apligraf functions similar to a skin graft when transplanted onto nude mice. *In vitro* studies suggest that following physical injury (---b(4)----------), the keratinocytes within Apligraf migrate, re-epithelialize, and keratinize. In addition, Apligraf secreted growth factors into the ----b(4)----------
---------- *In vivo* transplantation of Apligraf onto full-thickness cutaneous wounds in nude mice resulted in graft integration with the host tissue and persistence of the human keratinocytes and fibroblasts for one year.

Gintuit transplants on cutaneous wounds in nude mice suggest compatibility with periodontal dressings (i.e., Barricaid and Coe-Pak) and with 0.12% chlorhexidine solution (an anti-microbial agent).

The allogeneic human keratinocytes and dermal fibroblasts in Apligraf did not appear to induce an alloimmune response when evaluated by the -----b(4)---------- assay. The potential for Apligraf to induce an alloimmune response by indirect allorecognition was not evaluated.

Biocompatibility testing of Apligraf was conducted in conformance to ISO-10993 standards. Tests performed included: 1) general safety test; 2) cytotoxicity; 3) sensitization; 4) intracutaneous reactivity/irritation; 5) systemic toxicity (acute and subacute); 6) subchronic toxicity; and 7) hemocompatibility. This testing paradigm did not reveal any findings of significant biological concern. Subcutaneous administration of Apligraf into rabbits resulted in implantation site reactions, likely due to the xenogeneic immune response.

The toxicology study designs as discussed in the International Conference on Harmonisation (ICH) Safety ('S') guidelines, consisting of pharmacokinetics, acute toxicology, chronic toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity, safety pharmacology, and immunotoxicity (http://www.ich.org/cache/compo/276-254-1.html) were not conducted due to the nature of Gintuit and the extensive clinical experience with Apligraf.

5. Clinical Pharmacology

Drug Interactions

There have been no studies of drug interactions with Gintuit.

Mechanism of Action

Gintuit does not function as a tissue graft (i.e., Gintuit does not replace the missing keratinized tissue of the gingiva). There are insufficient data to determine the duration that Gintuit keratinocytes and fibroblasts survive *in vivo*. The mechanism of action by which Gintuit increases keratinized tissue at the treated site has not been identified.

6. Clinical / Statistical

a) Clinical Program

The results discussed in this section are based on the clinical and statistical reviews submitted to the file.

The BLA included study reports from two clinical studies (Study 05-PER-001 and Study 06-PER-002) for topical (non-submerged) application of Gintuit, and from Study 07-PER-004 for the submerged (under a flap) application of Gintuit. These studies evaluated the efficacy and safety of Gintuit for the treatment of gingival recession-type defects.

The trials were regulated by the US Food and Drug Administration (FDA), Center for Devices and Radiological Health (CDRH).

The data supporting efficacy claims were derived from Study 06-PER-002 (96 subjects enrolled and treated; 11 subjects in a training cohort; n=85 for efficacy analysis; n=96 for safety analysis). Study 06-PER-002 was conducted at four sites in the US from October 15, 2007 to December 8, 2008.

The overall design of Study 05-PER-001 was similar to the design of the subsequent Study 06-PER-002. Therefore, the efficacy results from Study 05-PER-001 are relevant to the proposed clinical indication and are presented in this review.

The third study, Study 07-PER-004, provides additional information on the safety of Gintuit in the oral environment.

Study 05-PER-001 (n=22 for efficacy analysis; n=25 for safety analysis)

Design

Study 05-PER-001 was a randomized, within-subject controlled (matched for teeth and condition of the gingiva), single-center trial. Subjects were adults with insufficient attached gingiva that required soft tissue grafting. Each subject received Gintuit and a free gingival graft (FGG; control treatment), using donor graft tissue from the subject's palate, with placement sites randomized to two non-adjacent teeth on contralateral sides of the same jaw. The study treatment did not include root coverage or treating the underlying condition. The study was designed to assess non-inferiority between treatment and control (FGG) in the change in the amount of attached gingiva (AG) over six months as the primary efficacy endpoint. The non-inferiority margin was a 1-mm difference in the change in gingival attachment between Gintuit and control. Keratinized tissue (KT) width was one of the eight secondary clinical efficacy endpoints for the study.

Results

Three of the 25 subjects participated as training subjects and were not included in the efficacy analysis. All subjects completed the study. Subjects were predominantly White (86%), female (68%), and had a mean age of 50 years (range, 31-70).

At six months, Gintuit sites in 14/22 (63.6%) subjects showed an increase in attached gingiva compared to baseline, while 21/22 (95%) of control sites showed an increase in attached gingiva. The mean increase in the amount of attached gingiva at Month 6 was 0.85 mm (0.48, 1.21) for Gintuit sites and 2.43 mm (2.06, 2.79) for control sites. Thus, Gintuit failed to demonstrate non-inferiority to control for the primary efficacy endpoint.

Keratinized tissue (KT) width was one of the secondary endpoints for the study. At six months, ≥ 2 mm of KT width was established in 18/22 (81.8%) Gintuit sites and in 22/22 (100%) control sites. There was a larger change from baseline to six months in the width

of keratinized tissue in the control sites compared to the Gintuit sites: the mean increase in KT width was 1.37 mm (95% CI: 0.97, 1.77) at Gintuit sites and 3.33 mm (95% CI: 2.93, 3.74) at control sites.

Based on these results, the Applicant selected the amount of KT as the primary outcome measure for the subsequent Study 06-PER-002.

Study 06-PER-002 (n=85 for efficacy analysis; n=96 for safety analysis)

Design

Study 06-PER-002 was a randomized, within-subject controlled (matched for teeth and condition of the gingiva), multicenter (four sites in the US) study. The study design and treatment procedure were similar to those used in Study 05-PER-001. The primary efficacy endpoint in Study 06-PER-002 was the percentage of Gintuit sites with KT ≥ 2 mm at six months, compared to a 50% success rate, in a single-arm comparison.

There were six secondary efficacy endpoints, for which the order of testing was pre-specified and conducted sequentially.

Results

Eleven of the 96 subjects were training subjects and were not included in the efficacy analysis. All subjects completed the study. Subjects were predominantly White (91%), female (54%), and had a mean age of 47 years (range, 18-71).

Eighty-one of the 85 subjects (95.3%) met success criteria of ≥ 2 mm KT at the Gintuit site (exact binomial 95% CI: 88.4%, 98.7%) at six months. The mean KT width increase at the Gintuit site was 3.21 mm, with a range of 1 to 6 mm (See Table 2). All 96 subjects met the primary endpoint at the control site. The success rate at the Gintuit site was not compared to the success rate at the control site.

Table 2. Primary Efficacy Endpoint (KT ≥ 2 mm at the Gintuit site at 6 months), Study 06-PER-002

Month 6	Statistics	Gintuit
	n	85
Subjects with KT width ≥ 2 mm	n (%) 95% CI p-value*	81 (95.3%) (88.4, 98.7) < 0.001*
KT width (mm)	Mean (SD) Median Min., Max.	3.21 (1.14) 3.0 1.0, 6.0

* Comparison to a pre-defined standard of 50% of subjects with KT width ≥2 mm.

The study found superiority of Gintuit to control in three of the six secondary endpoints: color matching, texture matching, and patient preference. The proportion of Gintuit sites with KT ≥ 1 mm was also significantly greater than a pre-defined success standard of 80%. There was no significant difference in surgical site sensitivity, the fifth secondary endpoint. Therefore, the absence of pain after three days, the sixth secondary endpoint, was not tested statistically. Although the pain measurement outcome was not tested statistically, results showed no important differences between Gintuit and control sites in this outcome.

Study 07-PER-004 (n=15 for safety analysis)

In a third oral indication study (Study 07-PER-004; n=15), Gintuit was evaluated for safety and preliminary effectiveness in a similar study design and study population. However, this study used a different surgical treatment procedure, in which Gintuit was placed under a flap (submerged) and root coverage was performed. Over the course of the study, there were two changes made in the surgical technique, resulting in three distinct groups of subjects, such that data could not be combined and analyzed for effectiveness. The study planned to enroll 25 subjects; the study was terminated after 15 subjects were enrolled and treated.

Efficacy Review Issues

- Based on the results of Study 05-PER-001, the amount of KT, rather than the amount of attached gingiva, was selected as the primary efficacy endpoint for Study 06-PER-002. However, the amount of attached gingiva is more clinically meaningful than the amount of KT. In addition, in Study 06-PER-002, the primary efficacy outcome of ≥ 2 mm KT at the Gintuit site was compared to a 50% success rate. The clinical meaningfulness of a 50% success rate is unclear. These issues of clinical meaningfulness were considered by an Advisory Committee. The Committee concluded that the study results, including the effect of Gintuit on KT, provided evidence of the effectiveness of Gintuit (see Section 8 *Advisory Committee Meeting*).

- Root coverage and Gintuit placement (non-submerged versus submerged) are relevant clinical issues for care providers. These issues have been addressed by revising the indication statement of the Prescribing Information to state that Gintuit is indicated for non-submerged application and that Gintuit is not intended to provide root coverage.

- The duration of treatment effect (beyond six months) and the efficacy of repeat applications of Gintuit in the oral environment have not been evaluated in clinical trials. These issues have been addressed by revising the Prescribing Information to inform care providers of these limitations of the available data.

- The efficacy of Gintuit has not been evaluated in children and has not been adequately evaluated in patients over age 65 years. These issues have been addressed by revising the Prescribing Information to inform care providers of the limitations of the available data in these populations. In addition, see Section 6.b. *Pediatrics* regarding a required postmarketing study in adolescents.

Bioresearch Monitoring, Data Quality, and Good Clinical Practices

Study subject enrollment for Study 06-PER-002, adherence to treatment, monitoring, and reporting procedures mandated by the protocol, data verification, investigators' financial interest disclosures, and geographic distribution were among the factors used by CBER's Bioresearch Monitoring Branch (BIMO), Division of Inspections and Surveillance, Office of Compliance and Biologics Quality (OCBQ) to select sites for inspection. Study 06-PER-002 was conducted at four sites in the US; the three sites that enrolled the most subjects were selected for inspection. Inspections for at least 15 subjects from each of the three sites were performed in support of this BLA. Results of the three site inspections are summarized in Table 3.

Table 3. BIMO Results of the Three Clinical Investigator Inspections

Study Site	Site #	Location	Number of Subjects Enrolled	FDA Form 483 Issued	Inspection Final Classification
Perio Health Professionals	010	Houston, TX	34 subjects	No	NAI*
University of Michigan School of Dentistry	016	Ann Arbor, MI	29 subjects	No	NAI
Boston Periodontics & Dental Implants	017	Boston, MA	30 subjects	No	NAI

* NAI: No Action Indicated

The BIMO inspections of the three clinical sites did not reveal any problem that could impact the overall results of the data reviewed.

Additionally, the clinical review team requested field investigators to obtain copies of treatment procedure operative notes from each of the three sites selected for inspection. A total of 59 operative notes, including at least 15 subjects from each of these sites, were audited. The clinical review of the 59 operative notes found that treatment procedures generally followed the surgical procedure described in the protocol; no significant deviations were identified.

Efficacy Conclusion

Based on the results of Studies 05-PER-001 and 06-PER-002, and considering the deliberations of the Advisory Committee, the review team concludes that the BLA contains substantial evidence of the effectiveness of Gintuit for the proposed indication.

b) Pediatrics

During the Advisory Committee (AC) meeting on November 17, 2011, Committee members stated that Gintuit would be used in adolescents with orthodontia-related gingival defects. Committee members also commented that Gintuit was unlikely to be used in children under the age of 12. Consequently, the Applicant submitted a request for a partial pediatric waiver for children less than 12 years of age. The Applicant also submitted a request for a deferral to conduct a postmarketing study to evaluate the safety and efficacy of Gintuit in adolescents ages 12 to 18 years. The requests for a partial pediatric waiver and a deferral of a postmarketing study were reviewed by the FDA Pediatric Review Committee (PeRC) on February 22, 2012. The PeRC recommended a partial waiver in patients ages birth through 11 years because mucogingival disorders are rare and/or do not exist in children in this age group. The PeRC recommended a deferral of a postmarketing study in patients ages 12 to 18 years because the product is ready for approval in adults.

The Applicant submitted a protocol synopsis for the postmarketing adolescent study, with the following due dates: to submit final study protocol by December 31, 2012; to complete the study by September 30, 2016; and to submit the final study report by March 31, 2017.

7. Safety

The safety data come from Studies 05-PER-001 and 06-PER-002 and a third study (Study 07-PER-004) that used a different application procedure (submerged under a flap). This BLA seeks approval of Gintuit for a non-submerged use; however, the submerged study provides additional safety information for Gintuit in the oral environment. There is also extensive safety information from postmarketing experience with Apligraf for chronic cutaneous wounds; the relevance of this Apligraf data to the oral indication was considered.

Studies 05-PER-001 and 06-PER-002 were randomized and within-subject controlled (i.e., each subject received both Gintuit and control treatment). The control treatment was a free gingival graft (FGG). The duration of the studies was six months following Gintuit application. Study 05-PER-001 was a single-center study (n=25) to evaluate the safety and efficacy of Gintuit in establishing a zone of attached gingiva (AG). Study 06-PER-002 was a multicenter study (n=96) to evaluate the safety and efficacy of Gintuit in establishing keratinized tissue (KT). The two study populations were similar.

Overall, 34% of subjects in Studies 05-PER-001 and 06-PER-002 had at least one adverse reaction. Table 4 lists all adverse reactions that occurred at an incidence of 1% or greater.

Table 4: Adverse Reactions Reported at Frequency of ≥ 1% (N=121)*

Reported Adverse Reaction (MedDRA Preferred Term)	Subjects n (%)	Events n
OVERALL	41 (34%)	65
Sinusitis	5 (4%)	6
Nasopharyngitis	2 (2%)	2
Respiratory Tract Infection	2 (2%)	2
Upper Respiratory Tract Infection	2 (2%)	2
Aphthous Stomatitis	2 (2%)	2
Oral Pain	2 (2%)	2
Mouth Injury	2 (2%)	2
Hypoaesthesia Facial	2 (2%)	2

* Studies 05-PER-001 and 06-PER-002

Local adverse reactions included gingival pain, gingival injury (due to inadvertent failure to remove a polycarbonate base from Gintuit before application), and ulcerations.

In Study 07-PER-004 (n=15), in which Gintuit was placed under a skin flap, adverse reactions included impaired healing, suture-related complications, mucosal erosion, and esophagitis.

There were no deaths, serious adverse reactions, malignancies, or serious immunologic adverse events due to Gintuit in any of the three studies.

The safety of Gintuit beyond six months was not evaluated in these clinical studies.

Postmarketing Experience with Apligraf

The following adverse events have been reported during post-approval use of Apligraf for the treatment of chronic cutaneous wounds. Since approval in 1998 through June 30, 2011, eleven medical device reports (MDRs) have been submitted to the FDA MAUDE safety database, within the categories of skin inflammation/blistering/erosion, wound infection, and cellulitis. Because these events are reported voluntarily by a population of uncertain size, and because there are no controls, it is not possible to determine their frequency in the exposed population or establish a causal relationship to exposure to Apligraf. In addition, the extent to which postmarketing safety data from Apligraf can be extrapolated to use of Gintuit in the oral environment is unclear. However, because of similarities in the products and their indications, there is a reasonable likelihood that adverse events that have been associated with Apligraf may also occur with oral use of Gintuit. Therefore, the Gintuit Prescribing Information informs care providers of these Apligraf postmarketing adverse reactions.

Safety Review Issue

As discussed above, there have been no malignancies attributed to Gintuit in any completed clinical trials or in the commercial use of Apligraf since its approval for the treatment of chronic cutaneous wounds. There have been no documented clinical or histological reports of tumor formation at the site of Gintuit application. However, tumorigenicity is a general concern for cellular therapies. In addition, karyotypic stability of the culture-expanded fibroblasts and keratinocytes was identified as a potential safety concern at the Advisory Committee meeting (see *Cell Bank Review Issues* in Section 3 *Chemistry, Manufacturing, and Controls*). To address this concern regarding malignancies, the review team recommends expedited reporting of malignancies identified after product approval.

8. Advisory Committee Meeting

The Cellular, Tissue, and Gene Therapies Advisory Committee (CTGT AC) met in open session on November 17, 2011. Topics covered included cell bank comparability, product potency, clinical effectiveness and safety of Gintuit, and statements describing the indication and intended patient population.

There were two discussion questions regarding product quality:

1. Please discuss the Applicant's approach to qualify and demonstrate comparability for new cell banks used for Gintuit manufacture.

   Discussion:
   The Committee stated that there are currently no data that demonstrate equivalence between cell banks and no correlative data between multiple cell banks and potency. The Committee recommended collecting more quantitative biological data (ex. amounts of cytokine expression) to support equivalent activity of product lots manufactured with different pairs of fibroblast and keratinocyte banks.

2. Please discuss the use of H&E staining as a product potency measure for Gintuit.

   Discussion:
   The Committee agreed that H&E staining is a good assay for the structural integrity of the product, however it is not an adequate, sensitive measure of biological activity. There are also little data to correlate histology with potency of the product. While the exact biological metric that is most appropriate for product potency remains unclear, most Committee Members felt that it would be appropriate to include cytokine assays given the current understanding of product function. Some Committee members suggested that a dynamic biologic assay (ex. animal model assay) would be more informative regarding product potency.

Clinical topics included clinical effectiveness, the indication statement, the patient population, and the safety of Gintuit for the proposed oral indication.

There were two voting questions:

3. Effectiveness: Based on the data provided, is Gintuit effective for the treatment of surgically created gingival surface defects in adults?

   Discussion:
   Members of the Committee agreed that the product was effective, in that it met the primary outcome of increasing the zone of keratinized tissue, and met four of the secondary endpoints, including color matching, texture matching, patient preference, and keratinized tissue ≥ 1 mm.

   Effectiveness voting: Yes: 15/15 voting members.

4. Safety: Do the data presented demonstrate the safety of Gintuit for the proposed indication?

   Discussion:
   Some Committee members thought that there could be safety issues related to possible inflammatory and immune responses, including the risk of tumorigenicity in at-risk populations, e.g., individuals at risk for oral cancer. Some members recommended safety follow-up of greater than 6 months to evaluate the risks of inflammation and tumorigenicity.

   Safety voting: Yes: 14; No: 1

Additional clinical discussion included the following:

There was no consensus regarding the precise patient population that would be appropriate for Gintuit. Committee members stated that the product could be indicated for aesthetic improvements in color and texture. Some Committee members stated that the product, if licensed, would be used in children and recommended conducting clinical trials in children with safety follow-up of greater than 6-months.

9. Other Relevant Regulatory Issues

Financial Disclosures

The Applicant declared that only one investigator or sub-investigator for Studies 05-PER-001 and 06-PER-002 had a financial agreement requiring disclosure. This investigator participated in all three studies of Gintuit for an oral indication. FDA statistical

examination of results from the investigator's site compared to other sites did not reveal any significant differences in efficacy results. The financial information submitted to the BLA was verified for the investigator during the BIMO inspection, and the site inspection revealed no deviations from applicable regulations.

10. Labeling

The proposed Prescribing Information (PI) has been reviewed and revised by the BLA review team. The most significant changes made by the review team are summarized below.

- The Indication statement has been revised to "Gintuit is an allogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. Gintuit is not intended to provide root coverage."
- Sections on Contraindications, Warnings and Precautions, and Adverse Reactions were modified according to FDA labeling guidelines.
- The Clinical Trials section was revised to include efficacy results from Study 05-PER-001.
- Tables and graphs depicting results of post-hoc efficacy analyses were deleted.
- The Clinical Pharmacology section was revised to state that the mechanism of action by which Gintuit increases keratinized tissue at the treated site has not been identified.

The review team concludes that the proposed PI provides adequate directions for the safe and effective use of Gintuit in the indicated population.

CBER's Advertising and Promotional Labeling Branch (APLB) found the proprietary name of Gintuit to be acceptable. In addition to the proprietary name, the APLB reviewed the PI and carton and container labels.

11. Recommendations and Risk / Benefit Assessment

a) Recommended Regulatory Action

The FDA review team recommends approval of Gintuit with the revised indication statement, "Gintuit is an allogeneic cellularized scaffold product indicated for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in adults. Gintuit is not intended to provide root coverage."

b) Risk / Benefit Assessment

The overall risk profile associated with Gintuit for topical application in the management of mucogingival conditions is acceptable in adults. The quality, efficacy, and safety of Gintuit have been reviewed and have been determined to be acceptable for use as indicated in the label.

c) Recommendation for Postmarketing Risk Management Activities

There has been no safety issue identified that warrants a Risk Evaluation and Mitigation Strategy (REMS). Gintuit is expected to have a favorable risk-benefit ratio when used as described in the label.

d) Recommendation for Postmarketing Activities

To address the safety concerns regarding malignancy, the review team recommends that Organogenesis Inc. submit expedited reports of any events in the MedDRA System Organ Class *Neoplasms benign, malignant and unspecified (including cysts and polyps)*, occurring at either the graft site or remote locations, within 15 days after learning of the event, through March 31, 2013.

PMR – Pediatric Clinical Study

The review team recommends a Postmarketing Requirement (PMR) under the Pediatric Research Equity Act (PREA) for Organogenesis Inc. to conduct a postmarketing study to evaluate the safety and effectiveness of Gintuit for topical (non-submerged) application to a surgically created vascular wound bed in the treatment of mucogingival conditions in pediatric patients 12 to 18 years of age. Organogenesis, Inc. has agreed to conduct this postmarketing study and has agreed to submit the final study protocol by December 31, 2012; to complete the study by September 30, 2016; and to submit the final study report by March 31, 2017.

PMC – CMC

The review team recommends five Postmarketing Commitments (PMCs) for Gintuit. In a letter received March 5, 2012, Organogenesis Inc. has agreed to the following:

1. ---b(4)---- ----------

    a. –b(4)---- ----------

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

c. ----b(4)--- ----------

d. ---b(4)---- ----------

2. -----b(4)-- ----------

3. ----b(4)--- ----------

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

5. ----b(4)----------