SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. General Information

Device Generic Name:	Interactive Wound Dressing
Device Trade Name:	Integra Dermal Regeneration Template Integra Omnigraft Dermal Regeneration Matrix
Device Procode:	MGR
Applicant:	Integra LifeSciences Corporation 311 Enterprise Drive Plainsboro, NJ 08536, USA
Date of Panel Recommendation:	None
Premarket Approval Application Number:	P900033/S042
Date of FDA Notice of Approval:	January 7, 2016
Expedited:	Not applicable

The original PMA (P900033), Integra Dermal Regeneration Template (Integra Template) was approved for postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient. Subsequently Integra Template was approved for the repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient (P900033/S008). The SSEDs to support these Indications for Use are available on the CDRH website and are incorporated by reference. The purpose of this supplement, S042, is to add a new Indication for Use, i.e., the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. Integra Template will also be marketed as Integra Omnigraft Dermal Regeneration Matrix (Omnigraft), specifically for the indication in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

II. INDICATION FOR USE

Integra® Omnigraft Dermal Regeneration Matrix is indicated for use in the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with

standard diabetic ulcer care.

Integra® Dermal Regeneration Template is indicated for the postexcisional treatment of life-threatening full-thickness or deep partial-thickness thermal injuries where sufficient autograft is not available at the time of excision or not desirable due to the physiological condition of the patient; repair of scar contractures when other therapies have failed or when donor sites for repair are not sufficient or desirable due to the physiological condition of the patient; and treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care.

III. CONTRAINDICATIONS

- This device should not be used in patients with known sensitivity to bovine collagen or chondroitin materials.

- Integra template should not be used on clinically diagnosed infected wounds.

IV. WARNINGS AND PRECAUTIONS

The Warnings and Precautions can be found in the Integra Dermal Regeneration Template and Integra Omnigraft Dermal Regeneration Matrix labeling.

V. DEVICE DESCRIPTION

Integra Template, available in meshed and non-meshed configurations, is an advanced bilayer matrix for dermal regeneration. The dermal replacement layer consists of a porous, three-dimensional matrix, comprised of bovine collagen and chondroitin-6-sulfate (C6S) that is designed with a controlled porosity and defined degradation rate. The temporary epidermal layer is made of a thin polysiloxane (silicone) layer to provide immediate wound coverage and control moisture loss from the wound.

Integra Template is provided sterile and non-pyrogenic. The inner foil pouch and product should be handled using sterile technique. Integra Template should not be re-sterilized.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The current standard of care for partial and full-thickness neuropathic diabetic foot ulcers is sharp debridement, moist wound therapy with daily wound care dressings, offloading, and infection control. For diabetic foot ulcers that are non-responsive to conventional therapy, alternative practices include skin substitutes, cellular or tissue derived products, or surgical alternatives such as arterial bypass grafting where vascular supply is insufficient and skin grafts.

VII. MARKETING HISTORY

Integra Template was first granted FDA Premarket Approval for use in life-threatening thermal injuries under PMA P900033 on March 1, 1996. On April 19, 2002, PMA

P900033 Supplement 008 was approved for an expanded indication for use (i.e., repair of scar contractures).

Integra Template was granted CE Mark approval in the European Union on March 20, 1998. The Integra product line is currently approved for marketing in the United States, European Union, Canada, Mexico, Argentina, Brazil, Colombia, Costa Rica, Peru, South Africa, Turkey, United Arab Emirates, Saudi Arabia, Israel, Egypt, Serbia, Jordan, Japan, New Zealand, Australia, and Singapore for use in partial and full thickness wounds and reconstructive surgery.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The safety of Integra Template for the treatment of partial and full-thickness neuropathic diabetic foot ulcers greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care was evaluated in a premarket clinical trial. Potential adverse events (e.g., complications) associated with the device and diabetic foot ulcer care, as reported in the clinical trial, include infection, worsening of ulcer, pain in extremity, cellulitis, osteomyelitis, edema peripheral, excoriation, upper respiratory trace infection, blister, influenza, pneumonia, vomiting, hypoglycemia, ingrown nail, urinary tract infection, erythema, cardiac failure congestive, pyrexia, diarrhea, hypertension, ulcer recurrence, local swelling, skin maceration, application site erosion, contusion, decubitus ulcer, nasopharyngitis, constipation, gastro-esophageal reflux disease, diabetic neuropathy, dizziness, asthma, cough, dyspnea, sinusitis, chest pain, hypotension, renal failure, blood glucose decreased, blood pressure increased, anxiety, arthralgia, laceration, abscess limb, gastritis, balance disorder, drug hypersensitivity, nail avulsion, sepsis, gout, muscle spasms, musculoskeletal pain, skin fissures, headache, coronary artery disease, visual impairment, anemia, localized infection, gangrene, diabetic ketoacidosis, limb injury, cataract, hyperlipidemia, skin ulcer, paronychia, skin infection, soft tissue infection, hypoesthesia, pulmonary embolism, and skin papilloma .

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

The preclinical testing performed in the original P900033 application was adequate to support the safety and effectiveness of the device for the treatment of partial and full-thickness neuropathic diabetic foot ulcers greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. No additional preclinical studies were submitted in this Panel Track Supplement.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The sponsor, i.e., Integra LifeSciences Corporation performed a clinical study to establish a reasonable assurance of safety and effectiveness for Integra Template for the treatment of partial and full-thickness neuropathic diabetic foot ulcers greater than six weeks in

duration with no capsule, tendon or bone exposed and no tunneling undermining or sinus tracts, when used in conjunction with standard diabetic ulcer care.

A. Study Design

Patients were enrolled and treated between April 1, 2010 and June 5, 2014. The database for this PMA reflects data collected through June 10, 2014 and includes 307 subjects who were randomized and received either Integra Template or Control treatment. There were 32 investigational sites \.

The clinical study IDRT/DFU US 2009-3 was a prospective, multi-center open-label, randomized (stratification by ulcer size) concurrently controlled pivotal clinical trial of subjects with partial or full thickness diabetic foot ulcers located distal to the malleolus with controlled diabetes and without significant compromise of arterial circulation. Subjects who met the entry criteria were enrolled in the two week Pre-Treatment Phase and followed while they received standard of care treatment (e.g., wound debridement, moist wound therapy with 0.9% Sodium Chloride gel) for the study ulcer, and appropriate secondary dressings as well as nutritional support and offloading/protective devices.

The primary safety endpoint was the incidence of adverse events recorded during the 16 week Treatment Phase and three monthly visits of the Follow-up Phase. Evaluations also included serum chemistry measurement (i.e., serum creatinine, blood urea nitrogen (BUN), serum glucose, HbA1c, pre-albumin and CBC with differential) at Pre-Treatment and the end of the Treatment Phase.

The primary effectiveness endpoint was the percentage of subjects with complete closure of the study ulcer as assessed by the Investigator, during the Treatment Phase.

1. Clinical Inclusion and Exclusion Criteria:

   Enrollment in IDRT/DFU US 2009-3 was limited to consented patients who met the following inclusion criteria: male or female of any race 18 years of age or older, females of childbearing potential with a negative urine pregnancy test result at baseline and practicing a reliable method of contraception throughout the study. All subjects were also required to have: Type I or Type II diabetes, HbA1c < 12%, a diabetic foot ulcer (DFU) that met all of the following criteria (i.e., full-thickness neuropathic DFU located distal to the malleolus (ankle) excluding ulcers between the toes, a minimum 2 cm margin between the qualifying ulcer and any other ulcer on the target foot, ulcer size ≥ 1 cm^2 and ≤ 12 cm^2, Wagner grade 1 or 2, depth ≤ 5 mm with no capsule, tendon or bone exposed and no tunneling undermining or sinus tracts and baseline ulcer duration at least 30 days at screening visit). Subjects also needed to have the ability to maintain the required offloading and applicable dressing changes as well as adequate vascular perfusion as defined by one of the following: (ABI ≥ 0.65 and ≤ 1.2, Toe pressure > 50 mm Hg, TcpO2 > 40 mm Hg or Doppler ultrasound consistent with adequate blood flow).

Patients were not permitted to enroll in IDRT/DFU US 2009-3 if they met any of the following exclusion criteria: suspected or confirmed signs of gangrene or wound infection on any part of the affected limb (subjects with wound infection at the Screening visit could be treated and subsequently re-screened for participation in the study after eradication of infection), history of hypersensitivity to bovine collagen and/or chondroitin, pregnant at the time of treatment, previously treated under this clinical study protocol, participated in another clinical study involving a device or a systematically administered investigational study drug or treatment within 30 days of randomization, currently receiving (within 30 days of the randomization visit) or was scheduled to receive medication within 30 days which was known to interfere with or affect the rate and quality of wound healing (e.g., steroid, immunosuppressive therapy, autoimmune disease therapy, allergenic therapy, cytostatic therapy), any of the following unstable conditions or circumstances that could interfere with treatment regimen compliance: the ability to perform required dressing changes, ability to comply with the treatment visit schedule, mental incapacity or current substance abuse, excessive lymphedema which could interfere with wound healing, active Charcot foot or Charcot foot with bony prominence that could inhibit wound healing, ulcers secondary to a disease other than diabetes, osteomyelitis with necrotic soft bone (if the Investigator suspected the presence of osteomyelitis, the diagnosis required confirmation by plain film X-ray), Chopart amputation, a history of bone cancer or metastatic disease of the affected limb, radiation therapy to the foot, or chemotherapy within the 12 months prior to randomization, treatment with wound dressings that included growth factors, engineered tissues, or skin substitutes (e.g., Regranex, Dermagraft, Apligraf, GraftJacket, OASIS, PriMatrix, or Matristem) within 30 days of randomization or was scheduled to receive these during the study, treated with hyperbaric oxygen within 5 days of Screening or was scheduled to receive this therapy during the study, a non-study ulcer that required a treatment other than moist wound therapy (i.e., the Standard of Care identified under this study), a history of or any of the following intercurrent illnesses or conditions that could compromise the safety of the subject or the normal wound healing process: end stage renal disease, immunosuppression, severe malnutrition, liver disease, aplastic anemia, scleroderma, acquired immune deficiency disease (AIDS) or Human Immunodeficiency Virus (HIV) positive, connective tissue disorder or exacerbation of sickle cell anemia, an employee or relative or any member of the Investigational site or the Sponsor or at the end of the Run-in period, and prior to Randomization, any of the following conditions: did not continue to meet the entrance criteria (inclusion and exclusion) above, or the size of the study ulcer, following debridement, had decreased by more than 30% from the baseline assessment measured at Screening.

2. <u>Follow-up Schedule</u>
   Prior to randomization, subjects entered a two week Screening/Run-in (Pre-Treatment) Phase during which subjects were treated with debridement and Standard of Care for diabetic foot ulcers. After the two-week Run-in period,

subjects whose ulcer size had decreased less than 30% and who continued to meet the eligibility criteria were randomized to either Active Treatment (Integra Template plus Standard of Care) or Control Treatment (Standard of Care) for the Treatment Phase of the study. During the Treatment Phase, subjects were treated and evaluated weekly for up to 16 weeks or until the study ulcer completely healed. Four weeks after either the study ulcer was confirmed completely healed or the final Treatment Visit (week 16), subjects entered the 12-week Follow-up Phase. During the Follow-up Phase, subjects attended monthly visits for safety and effectiveness outcomes, such as ulcer recurrence, adverse events and a Quality of Life Questionnaire.

3. Clinical Endpoints

The primary safety objective was to evaluate Integra Template safety through weekly assessments during the 16 week Treatment Phase and monthly visits during the three month Follow-up Phase. Evaluations included both monitoring for adverse events and changes in serum chemistry parameters (i.e., serum creatinine, blood urea nitrogen, serum glucose, HbA1c, pre-albumin and CBC with differential).

The primary effectiveness endpoint was the percentage of subjects with complete wound closure as assessed by the Investigator during the 16 week Treatment Phase. In the primary effectiveness analysis, the Last Observation Carried Forward principle was used for post-baseline time points with missing assessments. All subjects that discontinued before 100% wound closure during the Treatment Phase were not replaced and were considered treatment failures for the primary and secondary endpoint evaluations. Covariate analyses in the Intent-to-Treat population assessed the correlation of factors on ulcer healing and the robustness of the primary analysis, (i.e., baseline ulcer size, location and age, gender, baseline HbA1c, insulin use at baseline, diabetes type, race, smoking history, and baseline BMI).

The following additional effectiveness endpoints were evaluated during the Treatment Phase: 1) percentage of subjects with complete wound closure (assessed by computerized planimetry), 2) time to complete wound closure (assessed by the Investigator), 3) time to complete wound closure (assessed by computerized planimetry), 4) the rate of wound closure (assessed by computerized planimetry), 5) the incidence of study ulcer recurrence, determined during the Follow-up Phase, and 6) changes in the Quality of Life metrics, evaluated throughout the study.

B. Accountability of PMA Cohort

As illustrated in Table 1, 545 subjects were screened and 307 subjects were randomized to treatment.

Table 1 – Subject Disposition

Event	Integra	Control
Subjects screened	545	
Subjects randomized	307	
Subjects not randomized	238 (44%)	
Randomized Subjects	154	153
Completing Treatment Phase	128 (83.1%)	117 (76.5%)
Withdrawn during Treatment	26	36
Completed Follow-up	106 (68.8%)	82 (53.6%)
Withdrawn during Follow-up	22	35

The reasons that 238 subjects were enrolled and screened, but not randomized to treatment were: 83/238 (35%) had an ulcer heal more than 30% during the run-in period, 43/238 (18%) had ulcers that did not meet the size criteria, 31/238 (13%) had HbA1c greater than 12%, 21/238 (9%) had other reasons, 19/238 (8%) had an ongoing infection, 14/238 (6%) were non-compliant, 10/238 (4%) had a history of intercurrent illness/condition, 7/238 (3%) had osteomyelitis, 5/238 (2%) had an ulcer depth greater than 5mm, and 5/238 (2%) withdrew consent.

At the conclusion of the Treatment Phase of the trial, 128/154 (83.1%) of the Integra and 117/153 (76.5%) of the Control subjects remained on study. At the conclusion of the Treatment and Follow-Up Phases of the study, 106/154 (68.8%) Integra and 82/153 (53.6%) Control subjects completed the trial. The ramifications of the loss of 48/154 (31.2%) of the Integra and 71/153 (46.4%) of the Control subjects (or a total of 119/307 (38.8%) of the study participants is discussed below in the Other Analyses Section.

C. Study Population Demographics and Baseline Parameters

The baseline demographics in the Integra and Control arms were comparable for all parameters including, but not limited to, severity and type of diabetes, gender, race, age, and ulcer size area (Table 2).

Table 2 – ITT Baseline Population Demographics and Baseline Characteristics

Characteristic	Statistic	Integra (N = 154)	Control (N = 153)	Total (N = 307)
Age (years)	Mean (SD)	55.8 (10.6)	57.3 (9.7)	56.5 (10.1)
	Median	56.0	57.0	57.0
	Min, Max	31.0, 82.0	28.0, 82.0	28.0, 82.0
Gender	Male, n (n/N%)	118 (76.6)	114 (74.5)	232 (75.6)
	Female, n (n/N%)	36 (23.4)	39 (25.5)	75 (24.4)
Race	American Indian/Alaskan Native, n (n/N%)	0 (0.0)	2 (1.3)	2 (0.6)
	Asian, n (n/N%)	1 (0.6)	2 (1.3)	3 (1.0)
	Black Or African American, n (n/N%)	28 (18.2)	34 (22.1)	62 (20.1)

	Native Hawaiian or Pacific Islander, n (n/N%)	1 (0.6)	0 (0.0)	1 (0.3)
	Caucasian, n (n/N%)	118 (76.6)	111 (72.1)	229 (74.4)
	Other, n (n/N%)	6 (3.9)	5 (3.2)	11 (3.6)
Ethnicity	Not Hispanic/Latino, n (n/N%)	108 (70.1)	116 (75.8)	224 (73.0)
	Hispanic or Latino, n (n/N%)	46 (29.9)	37 (24.2)	83 (27.0)
Weight (kg)	Mean (SD)	107 (23.3)	107 (28.9)	107 (26.2)
	Median	105	103	104
	Min, Max	63.5, 178	52.2, 221	52.2, 221
Height (cm)	Mean (SD)	178 (9.4)	177 (12.2)	177 (10.9)
	Median	178	180	178
	Min, Max	154, 196	132, 203	132, 203
BMI (kg/m^2)	Mean (SD)	34.0 (7.2)	34.1 (8.4)	34.0 (7.8)
	Median	33.8	32.1	33.0
	Min, Max	21.4, 58.9	19.9, 62.4	19.9, 62.4
Tobacco Product Use	Yes, n (n/N%)	28 (18.2)	19 (12.4)	47 (15.3)
	No, n (n/N%)	126 (81.8)	134 (87.6)	260 (84.7)
Diabetes Mellitus Type	Type 1, n (n/N%)	4 (2.6)	13 (8.5)	17 (5.5)
	Type 2, n (n/N%)	150 (97.4)	140 (91.5)	290 (94.5
Use Of Insulin at Baseline	Yes, n (n/N%)	30 (19.5)	37 (24.2)	67 (21.8)
	No, n (n/N%)	124 (80.5)	116 (75.8)	240 (78.2)
Age Of Study Ulcer (Days)	n	154	153	307
	Mean (SD)	308 (491)	303 (418)	305 (455)
	Median	126	152	140
	Min, Max	31.0, 4501	32.0, 2059	31.0, 4501
% Reduction in Ulcer Area Size Between Screening & First Treatment Application	Mean (SD)	-14 (38.0)	-17 (65.9)	-16 (53.7)
	Median	-3.4	-1.6	-2.0
	Min, Max	-228, 29.2	-565, 28.6	-565, 29.2
Baseline Study Ulcer Size (cm^2)	Mean (SD)	3.53 (2.5)	3.65 (2.6)	3.59 (2.6)
	Median	2.6	2.6	2.6
	Min, Max	1.0, 11.5	1.0, 10.8	1.0, 11.5
Location of Study Ulcer	Plantar, n (n/N %)	126 (81.8)	127 (83.0)	253 (82.4)
	Dorsal, n (n/N %)	28 (18.1)	25 (16.3)	53 (17.3)
	Medial, n (n/N %)	0	1 (0.7)	1 (0.3)
Wagner Grade	Grade 1, n (n/N %)	45 (29.2)	37 (24.2)	82 (26.7)
	Grade 2, n (n/N %)	109 (70.8)	116 (75.8)	225 (73.3)

Number of Integra Template Applications – The median number of Integra Template applications was one (i.e., 92/154 (59.7%) subjects required a single Integra Template application). Table 3 provides a summary of the number of subjects and the number

of Integra Template applications required. Reapplications were at the discretion of the investigator. The most common reasons for reapplications were non-adherence with fluid accumulation and infection.

Table 3 – Summary of Subjects with Applications of Integra Template

No. of Applications	No. Integra Subjects N = 154 n (n/N %)
1	92 (59.7)
2	33 (21.4)
3	12 (7.8)
4	5 (3.2)
5	5 (3.2)
6	2 (1.3)
7	2 (1.3)
11	2 (1.3)
15	1 (0.6)

Offloading of the Study Ulcer **–** DFU offloading is a well-recognized method of promoting wound closure. Subject compliance in ulcer offloading was assessed via subject diary review and subject interviews. In this analysis, high levels of overall subject offloading compliance were observed for both Integra (i.e., mean = 21.6 hours/day) and Control subjects (i.e., mean = 20.9 hours / day). Given the limited number of subjects with low offloading compliance (i.e., 8/154 Integra and 11/153 Control subjects offloaded 0-14 hours / day), no significant correlation could be made between offloading compliance with incidence of healing, time to wound healing, and subject discontinuation.

D. Safety and Effectiveness Results

1. Safety Results

All Adverse Events (AEs) – 101/154 (65.6%) of Integra and 115/153 (75.2%) of Control subjects reported an AE. A total of 798 AEs were reported, with 444/798 (55.6%) AEs in Control subjects and 354/798 (44.4%) AEs in Integra subjects.

All AEs that were reported in the study at an incidence of greater than or equal to 1% in either cohort are presented in Table 4. This table reflects AEs that were both attributed and not attributed to treatment. They are also listed in descending order according to their frequency in the Integra cohort. There were no unanticipated AEs in the trial.

Table 4 – Adverse Events (Reported in ≥1% of Subjects) by MEDRA Preferred Term

Adverse event (Preferred Term)	Integra N = 154 Subjects n (n/N%)	Control N = 153 subjects n (n/N%)
Diabetic foot infection	23 (14.9)	23 (15.0)
Diabetic foot	22 (14.3)	31 (20.3)

Pain in extremity	14 (9.1)	20 (13.1)
Cellulitis	13 (8.4)	13 (8.5)
Osteomyelitis	9 (5.8)	19 (12.4)
Edema peripheral	7 (4.5)	7 (4.6)
Nausea	7 (4.5)	3 (2.0)
Condition aggravated	6 (3.9)	14 (9.2)
Excoriation	6 (3.9)	7 (4.6)
Upper respiratory tract infection	6 (3.9)	6 (3.9)
Blister	6 (3.9)	6 (3.9)
Influenza	5 (3.2)	3 (2.0)
Wound	4 (2.6)	6 (3.9)
Pneumonia	4 (2.6)	3 (2.0)
Vomiting	4 (2.6)	2 (1.3)
Hypoglycemia	4 (2.6)	1 (0.7)
Ingrowing nail	4 (2.6)	1 (0.7)
Urinary tract infection	3 (1.9)	6 (3.9)
Erythema	3 (1.9)	4 (2.6
Cardiac failure congestive	3 (1.9)	4 (2.6)
Pyrexia	3 (1.9)	3 (2.0)
Application site pain	3 (1.9)	2 (1.3)
Diarrhea	3 (1.9)	2 (1.3)
Hypertension	3 (1.9)	2 (1.3)
Disease recurrence	3 (1.9)	1 (0.7)
Local swelling	3 (1.9)	1 (0.7)
Skin maceration	3 (1.9)	1 (0.7)
Application site erosion	3 (1.9)	0
Contusion	3 (1.9)	0
Decubitus ulcer	2 (1.3)	4 (2.6)
Nasopharyngitis	2 (1.3)	2 (1.3)
Constipation	2 (1.3)	2 (1.3)
Gastrooesophageal reflux disease	2 (1.3)	2 (1.3)
Diabetic neuropathy	2 (1.3)	2 (1.3)
Dizziness	2 (1.3)	2 (1.3)
Asthma	2 (1.3)	2 (1.3)
Cough	2 (1.3)	2 (1.3)
Dyspnea	2 (1.3)	2 (1.3)
Pain	2 (1.3)	2 (1.3)
Sinusitis	2 (1.3)	1 (0.7)
Chest pain	2 (1.3)	1 (0.7)
Hypotension	2 (1.3)	0
Renal failure	2 (1.3)	0
Blood glucose decreased	2 (1.3)	0
Blood pressure increased	2 (1.3)	0
Anxiety	2 (1.3)	0
Arthralgia	1 (0.6)	6 (3.9)
Laceration	1 (0.6)	5 (3.3)
Abscess limb	1 (0.6)	4 (2.6)
Gastritis	1 (0.6)	3 (2.0)
Balance disorder	1 (0.6)	3 (2.0)
Drug hypersensitivity	1 (0.6)	3 (2.0)
Nail avulsion	1 (0.6)	2 (1.3)
Sepsis	1 (0.6)	2 (1.3)

Gout	1 (0.6)	2 (1.3)
Muscle spasms	1 (0.6)	2 (1.3)
Musculoskeletal pain	1 (0.6)	2 (1.3)
Skin fissures	1 (0.6)	2 (1.3)
Headache	1 (0.6)	2 (1.3)
Coronary artery disease	1 (0.6)	2 (1.3)
Visual impairment	1 (0.6)	2 (1.3)
Anemia	1 (0.6)	2 (1.3)
Localized infection	0	4 (2.6)
Gangrene	0	3 (2.0)
Diabetes mellitus	0	3 (2.0)
Diabetic ketoacidosis	0	3 (2.0)
Limb injury	0	3 (2.0)
Cataract	0	3 (2.0)
Hyperlipidemia	0	2 (1.3)
Skin ulcer	0	2 (1.3)
Paronychia	0	2 (1.3)
Skin infection	0	2 (1.3)
Soft tissue infection	0	2 (1.3)
Hypoesthesia	0	2 (1.3)
Pulmonary embolism	0	2 (1.3)
Skin papilloma	0	2 (1.3)

Serious Adverse Events (SAEs) – 38/154 (24.7%) of the Integra and 55/153 (35.9%) of the Control subjects reported a SAE. The incidence of serious infections and infestations was 27/154 (17.5%) in the Integra and 40/153 (26.1%) in the Control cohorts. Osteomyelitis was the most common SAE infection (i.e., 8/154 (5.2%) of the Integra and 15/153 (9.8%) of the Control subjects).

Adverse Events potentially related to treatment (TRAE) - occurred in 7/154 (4.5%) of the Integra and 8/153 (5.2%) of the Control subjects. In the Integra group, the 11 TRAE incidences were: diabetic foot infections (3.2%; 5/154), application site cellulitis (0.6%; 1/154), cellulitis (0.6%; 1/154), infected skin ulcer (0.6%; 1/154), sepsis (0.6%; 1/154), application site erythema (0.6%; 1/154), and excoriation (0.6%; 1/154). Four incidences, occurring in two subjects, were also Serious Adverse Events (i.e., sepsis, diabetic foot infection, cellulitis, and infected skin ulcer). These serious, potentially related AEs resulted in the two Integra subjects being withdrawn from the clinical trial. In the Control group, the 17 TRAEs were: application site odor (0.7%; 1/153), arthralgia (0.7%; 1/153), condition aggravated (1.3%; 2/153), dermatitis atopic (0.7%; 1/153), diabetic foot (1.3%; 2/153), laceration (0.7%; 1/153), neuropathic arthropathy (0.7%; 1/153), edema peripheral (0.7%; 1/153), osteomyelitis (0.7%; 1/153), pain in extremity (0.7%; 1/153), skin papilloma (0.7%; 1/153), urinary tract infection (0.7%; 1/153), and wound (0.7%; 1/153). None of the 17 potentially related AEs in the Control group were considered Serious Adverse Events; however, one subject in the Control group was withdrawn from the clinical trial due to a potentially related adverse event (i.e. osteomyelitis). All other Integra and Control subjects who

withdrew from the clinical trial due to AEs had events that were judged unlikely or not related to the study treatment.

Patient Death – Four Control subjects and zero Integra subjects died during the study. All deaths were judged unrelated to the Study Treatment.

Chemical Labs – Serum Chemistry Values for all Subjects (i.e., range, mean and median values) were comparable between the two treatment groups at both baseline and the end of treatment. None of the subjects in this trial had the treatment discontinued or the trial terminated due to laboratory abnormalities. Changes in the serum chemistry that were deemed clinically significant by the Investigators were reported as adverse events. One Integra and one Control subject experienced SAEs reported as hypoglycemia. None of these events were judged related to the Study Treatment.

2. Effectiveness results

Primary Effectiveness Endpoint

The primary effectiveness endpoint was complete closure of the study ulcer, as assessed by the investigator, during the 16-week Treatment Phase. 79/154 (51.3%) of the Integra and 49/153 (32.0%) of the Control subjects achieved 100% complete closure of the study ulcer. This 19.3% treatment difference was statistically significant (p-value = 0.0007).

Secondary Effectiveness Outcomes

Complete Wound Closure – Computerized Planimetry – During the Treatment Phase, 77/154 (50.0%) of the Integra and 48/153 (31.4%) of the Control subjects achieved 100% complete wound closure as assessed by Computerized Planimetry. The treatment difference of 18.6% was statistically significant (p=0.0010) and a strong agreement with the Primary Effectiveness endpoint was observed.

Time to Complete Wound Closure – Investigator's Assessment – The Kaplan-Meier results for the Investigator Assessment of time to complete wound closure demonstrated that: 1) approximately 50% of the IDRT subjects achieved complete wound closure by day 85, whereas only 32% of the Control subjects achieved complete wound closure at the end of the Treatment Phase (Day 112); 2) a 49 day difference existed in the time needed to achieve complete healing for 25% of all subjects (i.e., 43 days for IDRT and 92 days for Control subjects); and 3) the median time to complete wound closure for Integra subjects (43 days) was 35 days shorter than Control subjects (78 days).

Time to Complete Wound Closure – Computerized Planimetry – Results similar to the Investigator Assessment of time to complete wound closure were observed,

i.e., 1) 99 days were required for approximately 50% of the IDRT subjects to achieve complete wound closure; 2) a 49 day difference existed in the time needed to achieve complete healing in 25% of all subjects (i.e., 43 days for IDRT and 92 days for Control subjects); and 3) the median time to complete wound closure for Integra subjects (43 days) was 35 days shorter than Control subjects (78 days).

Rate of Wound Size Reduction – The rate of wound healing (% healed/week) or rate of wound size reduction was measured via planimetric assessment (during the Treatment Phase) and calculated with the following formula:

Rate (% healed/week) =
7 * [(Baseline wound size) – (Post-baseline wound size)] /
[(Baseline wound size) * (days in clinical trial)]

The average wound size at baseline was 3.53 cm^2 for Integra and 3.65 cm^2 for Control subjects. The rate of wound size reduction observed at the end of the Treatment Phase for Integra and Control subjects was 7.15% healed/week and 4.81% healed/week, respectively (p=0.0115).

Incidence of Ulcer Recurrence – 15/79 (19.0%) of the healed Integra and 13/49 (26.5%) of the healed Control subjects experienced ulcer recurrence during the study. The difference was not statistically significant.

Change in Baseline Quality of Life Metrics at the End of Treatment – Integra subjects showed significant improvements in: 1) the Physical Functioning for daily activities of walking, climbing stairs, bending, bathing, carrying groceries, and moderate to vigorous activities and 2) the Reduction in the Bodily Pain (and/or limitations of normal work activities due to pain) Modules of the Quality of Life Questionnaire SF-36v2 Health Survey, compared to Control subjects. No significant differences between treatment groups were observed for the other Modules in the Quality of Life Questionnaire SF-36v2 Health Survey (i.e., General Health, Social Functioning, Role Emotional, Mental Health or Vitality).

3. Subgroup Analyses

Covariate Analyses – Two factors in the ITT Population, i.e., baseline wound size (p = 0.0009) and study ulcer age (p = 0.0014), were significant contributing factors to ulcer healing. Diabetes Mellitus Type, baseline HbA1c, race, baseline BMI, wound location (left or right foot), tobacco use, age, ethnicity, Wagner Grade, ulcer location (plantar/dorsal/medial), insulin use, or gender were not significant factors to wound healing. All analysis models for the primary and secondary endpoints were adjusted for the baseline wound size and the baseline age of ulcer.

Fenestrated vs. Non-Fenestrated Integra Template – Fenestrating and meshing (at a 1:1 ratio) of Integra Template was permitted (at the discretion of the investigator) to allow for drainage in the presence of exudate or hematoma. Based on CRF review: 1) no subjects received meshed Integra Template, 2) 122 subjects had fenestrated Integra Template applied at one or more visits, 3) 33 subjects received neither meshed nor fenestrated Integra Template, 4) one subject had both fenestrated and non-cut Integra Template at different visits and is counted in both subgroups, 5) 65/122 (53.28%) of the subjects receiving fenestrated Integra Template achieved complete wound closure, 6) 14/33 (42.42%) of the subjects receiving non-fenestrated Integra Template achieved wound closure, and 7) 32.03% of the Control group achieved wound closure.

Poolability of Sites – Site poolability was assessed prior to pooling the data from the different investigational sites. The results of this analysis demonstrated that the effect of site was not statistically significant and the overall results for complete wound closure were not site-dependent.

Subject Withdrawal from the Study – The reasons for subject withdrawal/discontinuation from the Treatment, and Study (i.e., Treatment + Follow-up Phases) are presented in Tables 5 and 6, respectively.

Table 5 – Reasons for Subject Withdrawal from Treatment Phase

Premature Termination Reason	**Integra** N = 154 n (n/N %)	**Control** N = 153 n (n/N %)	**Total** N = 307 n (n/N %)
Adverse Event	13 (8.4%)	16 (10.5%)	29 (9.4%)
Investigator's decision	8 (5.2%)	8 (5.2%)	16 (5.2%)
Subject withdrew consent	1 (0.6%)	6 (3.9%)	7 (2.3%)
Protocol violation	2 (1.3%)	2 (1.3%)	4 (1.3%)
Lost-to-follow-up	1 (0.6%)	2 (1.3%)	3 (1.0%)
Other	1 (0.6%)	2 (1.3%)	3 (1.0%)
Total	26 (16.9%)	36 (23.5%)	62 (20.2%)

Table 6 – Reasons for Subject Withdrawal from Study (Treatment + Follow-up Phases)

Premature Termination Reason	**Integra** N = 154 n (n/N %)	**Control** N = 153 n (n/N %)	**Total** N = 307 n (n/N %)
Adverse Event	13 (8.4%)	25 (16.3%)	38 (12.4%)
Investigator's decision	14 (9.1%)	16 (10.5%)	30 (9.8%)
Lost-to-follow-up	9 (5.8%)	11 (7.2%)	20 (6.5%)
Other	6 (3.9%)	7 (4.6%)	13 (4.2%)
Subject withdrew	3 (1.9%)	9 (5.9%)	12 (3.9%)

consent			
Protocol violation	3 (1.9%)	3 (2.0%)	6 (2.0%)
Total	48 (31.2%)	71 (46.4%)	119 (38.8%)

The impact of subject withdrawals on the validity of the clinical study was analyzed as discussed below.

Demographics of the Withdrawn Population were compared and no evidence of selection bias in subject withdrawal was observed. These analyses included comparisons of the following factors for Integra and Control cohorts who withdrew during the Treatment Phase: 1) baseline study ulcer size, 2) the mean wound size reduction during the two week Run-In period, 3) the proportion of plantar to dorsal wounds and 4) baseline ulcer severity (i.e., ratio of Grade 1 to Grade 2 ulcers). The average baseline ulcer duration of Control subjects who withdrew during the Treatment Phase was longer than Integra subjects (i.e., a mean value of 254 days for Integra and 368 days for Control subjects).

Based on the computerized planimetry assessment prior to subject withdrawal during the treatment phase, a majority of withdrawals were due to the lack of treatment effectiveness in both groups, and the observed higher percentage of withdrawal in the control group appeared to be a reflection of the inferior performance of the Control treatment as compared to the Integra treatment. Also, no significant association between the treatment groups and subject discontinuation was observed for: 1) subjects with a history of lower extremity amputation and discontinuation during the Treatment Phase, 2) subjects with a history of cellulitis and discontinuation during the Treatment Phase, 3) subjects without a history of lower extremity infection and discontinuation during the Treatment Phase, 4) subjects with an additional ulcer at study entry and discontinuation during the Treatment Phase, 5) subjects with a prior history of foot surgery and discontinuation during the Treatment Phase, 6) the time that a subject remained on study prior to withdrawal, 7) the number of subjects who withdrew from the study during the Treatment Phase and experienced at least one major protocol deviation, 8) the amount of daily offloading or 9) the frequency of AEs and SAEs in both treatment cohorts. Therefore, the loss of these subjects did not significantly alter the evaluation of device safety or effectiveness.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 35 Principal Investigators and 80 Sub-Investigators at sites that randomized subjects. None of the Principal or Sub Investigators had disclosable

financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

- **Relevant Post Market Experience**

Since March 01, 1996, Integra Template has been sold for the treatment of life-threatening full-thickness or deep partial-thickness thermal injuries, and since April 19, 2002 Integra Template has also been sold for the repair of scar contractures. Integra Bilayer Matrix Wound Dressing (which has the same composition as Integra Template) was cleared on August 14, 2002 for the management of partial and full thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, surgical wounds (donor sites / grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations. second-degree burns, and skin tears) and draining wounds. Integra Wound Matrix Dressing (which contains the same dermal layer, but not the silicone layer of Integra Template), was cleared on September 10, 2002 for the same indications as the Integra Bilayer Matrix Wound Dressing. Integra Wound Matrix (Thin) (which has the same, but thinner composition as Integra Wound Matrix Dressing) was cleared on February 9, 2012 for management of wounds including: partial and full-thickness wounds, pressure ulcers, venous ulcers, diabetic ulcers, chronic vascular ulcers, tunneled/undermined wounds, surgical wounds (donor sites/grafts, post-Moh's surgery, post-laser surgery, podiatric, wound dehiscence), trauma wounds (abrasions, lacerations, second-degree bums, skin tears) and draining wounds.

Since 1996, 111 clinical Medical Device Reports (MDRs) were submitted to the sponsor, and these are summarized in Table 7.

Table 7 – Summary of Clinical MDRs of Integra Product Family Since 1996

MDR Category	**Total MDRs**
Infection	60
Poor Take/Dislodgment	18
Allergic Reaction	6
Autograft Lost	4
Wound Dehiscence	4
Regeneration of Granulous Skin	3
Death*	3
No Autograft Take	3
Non healing Wound	2
Matrix Calcification	2
Septic Shock	1
Hematoma	1
Fever	1
Hypertrophic Scarring	1
Bulging of Graft	1
Factor 5 Deficiency**	1
Total	**111**

* The three deaths that Integra filed as MDRs were deemed by the physicians who reported the complaints to be unrelated to the Integra template.

** Integra investigators determined that Factor 5 Deficiency could not have been caused by the Integra product. The complaint was filed because a physician thought that the product could have caused the deficiency based on his research that bovine thrombin has been known to cause the deficiency. However, Integra products do not contain bovine thrombin.

XII. PANEL RECOMMENDATIONS

Pursuant to section 515(c)(2) of the Food, Drug and Cosmetic Act (the Act) as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the General and Plastic Surgery Panel and FDA advisory panel for review and recommendation. This is because the information in this PMA supplement substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROMPRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Assessment of product effectiveness is based on the results of Pivotal Clinical Trial IDRT/DFU US 2009-3. The submitted data provided a reasonable assurance that the device is effective for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. The specific conclusions are:

- The study met the pre-specified primary effectiveness criterion of complete study ulcer closure, (as assessed by the investigator during the 16-week treatment period). 79/154 (51.3%) of the Integra and 49/153 (32.0%) of the Control subjects achieved complete wound closure. This 19.3% treatment difference was statistically significant (p-value = 0.0007). 245/307 (79.8%) of the subjects were evaluated for this primary effectiveness endpoint.

- The study met the following pre-specified secondary effectiveness endpoints. Specifically, Integra Template was statistically superior in the: 1) percentage of subjects with complete study ulcer closure, as assessed by computerized planimetry, (i.e., 77/154 (50.0%) of the Integra vs 48/153 (31.4%;) of the Control subjects, p=0.0010); 2) the time to complete wound closure as assessed by the Investigator (i.e., the median time to complete wound closure for Integra subjects (43 days) was 35 days shorter than Control subjects (78 days); 3) the time to complete wound closure as assessed by computerized planimetry; (i.e., the same results were observed by computerized planimetry and Investigator assessment); and 4) the wound closure rate as assessed by computerized planimetry (i.e., the average rate of wound size reduction was 7.15% (Integra) and 4.81% (Control) healed/week), p=0.0115.

- The incidence of ulcer recurrence, although not statistically significant, was less in the healed Integra Template cohort 15/79 (19.0%) than the healed Control subject cohort 13/49 (26.5%).

- Omnigraft subjects showed improvement in the Physical Functioning for Daily Activities and Reduction in the Bodily Pain modules of the Quality of Life Questionnaire SF-36v2 Health Survey questionnaire. No significant differences between treatment groups were observed for General Health, Social Functioning, Role Emotional, Mental Health or Vitality Modules of this questionnaire.

- Review of baseline demographics and wound conditions, indicated that the two cohorts were well balanced. With the exception of baseline ulcer size and baseline ulcer age, no other study covariate (i.e., Diabetes Mellitus Type, baseline HbA1c, race, baseline BMI, wound location (left or right foot), tobacco use, patient age (continuous), patient age (cutoff 65 years), ethnicity, Wagner Grade, Insulin use, gender, and ulcer location (plantar/dorsal/medial) influenced the clinical effectiveness outcomes measured. This observation is consistent with previous clinical studies of diabetic neuropathic foot ulcers.

B. <u>Safety Conclusions</u>

The adverse effects of the device are based on data collected in the Pivotal Study IDRT/DFU US 2009-3 to support PMA approval, as described above, as well as an evaluation of the Post Market Surveillance reports. The submitted data provided a reasonable assurance that the device is safe for the treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration, with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care. The specific conclusions are:

- Safety assessments included clinical visits during the two week Pre-Treatment Phase, weekly assessments during the 16 week Treatment Phase, and monthly assessments during the three month Follow-up Phase. Serum chemistry parameters were also determined at baseline and the end of the Treatment Phase.

- 101/154 (65.6%) of the Integra and 115/153 (75.2%) of the Control subjects reported an adverse event (AE). Of the total 798 AEs reported in the study, 354/798 (44.4%) occurred in Integra and 444/798 (55.6%) occurred in Control subjects. Integra subjects experienced fewer AEs than Control subjects.

- 38/154 (24.7%) of the Integra and 55/153 (35.9%) of the Control subjects reported a serious adverse event (SAE). Integra subjects experienced fewer SAEs than Control subjects.

- Adverse Events that were potentially related to treatment (TRAE) occurred in 7/154 (4.5%) of the Integra and 8/153 (5.2%) of the Control subjects. In the Integra group, the TRAEs were: diabetic foot infections (3.2%; 5/154), application

site cellulitis (0.6%; 1/154), cellulitis (0.6%; 1/154), infected skin ulcer (0.6%; 1/154), sepsis (0.6%; 1/154), application site erythema (0.6%; 1/154), and excoriation (0.6%; 1/154). In the Control group, the TRAEs were: application site odor (0.7%; 1/153), arthralgia (0.7%; 1/153), condition aggravated (1.3%; 2/153), dermatitis atopic (0.7%; 1/153), diabetic foot (1.3%; 2/153), laceration (0.7%; 1/153), neuropathic arthropathy (0.7%; 1/153), edema peripheral (0.7%; 1/153), osteomyelitis (0.7%; 1/153), pain in extremity (0.7%; 1/153), skin papilloma (0.7%; 1/153), urinary tract infection (0.7%; 1/153), and wound (0.7%; 1/153).

- The most common AE in the study was infection. 56/154 (36.4%) of Integra subjects experienced an infection or infestation, 26/56 (46.4%) of these subjects healed and 11/56 (19.6%) of these subjects went on to amputation. 74/153 (48.4%) of Control subjects experienced an infection or infestation, 19/74 (25.7%) of these subjects healed and 16/74 (21.6%) of these subjects went on to amputation. The incidence of SAEs infections and infestations was 27/154 (17.5%) in the Integra and 40/153 (26.1%) in the Control cohorts. Osteomyelitis was the most common SAE infection. This SAE occurred in 8/154 (5.2%) of the Integra and 15/153 (9.8%) of the Control subjects.

- Four Control subjects died during the study of causes unrelated to study treatment. No patient deaths occurred in the Integra cohort.

- Recognizing the limitations associated with reviewing safety information in the Integra LifeSciences Corporation Postmarketing Safety database, it appears that the types and incidence of adverse events observed with Integra (and similar products) are reported at a low level and do not raise any concerns for the proposed indication for use. Since the product has been on the market in various forms since 1996, it is also unlikely that further post market experience will provide different information as to safety of the device. Furthermore, there is no reason to expect that "real-world" experience will differ. Thus, the safety profile of Integra Template in seriously burned patients for the past 19 years was an important consideration.

C. Benefit-Risk Conclusion

The impact of diabetic foot ulcers (DFU) on individuals and society is significant. Failure to respond to local wound care in DFU will usually result in amputation. If wound closure can be achieved, it is likely to delay the need for surgical intervention and offer other benefits such as improvements in: productivity, mental outlook, social interactions, and time at work, as well as decreased mortality.

The benefits of Omnigraft observed in this study were improved ulcer healing rates and patient condition. The risks associated with this product are well known and no new or unexpected risks were identified during the trial in this population. The safety and efficacy of this product in this population was superior to standard of care.

In conclusion, given the available information above, the data demonstrate that for treatment of partial and full-thickness neuropathic diabetic foot ulcers that are greater than six weeks in duration with no capsule, tendon or bone exposed, when used in conjunction with standard diabetic ulcer care, that the probable benefits outweigh the probable risks when used in accordance with the indications for use.

D. Overall Conclusion

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH Decision

CDRH issued an approval order on January 7, 2016.

XV. Approval Specifications

Directions for Use: See product labeling.

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, and Precautions, Adverse Reactions in the device labeling.

Postapproval Requirement and Restrictions: See the approval order.