

## **SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)**

### **I. GENERAL INFORMATION**

Device Generic Name: Mechanical and enzymatic autologous skin processor for preparing cell suspension, with applicator.

Device Trade Name: RECELL® Autologous Cell Harvesting Device

Device Procode: QCZ

Applicant's Name and Address: AVITA Medical Americas, LLC.  
28159 Avenue Stanford, Suite 220  
Valencia, CA 91355

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: BP170122/575

Date of FDA Notice of Approval: December 22, 2023

Priority Review: Granted October 27, 2017

Expedited Access Pathway (EAP): Granted EAP designation status on December 10, 2015 because the device provides for more effective treatment of a life-threatening condition and its availability is in the best interest of patients.

Breakthrough Device Designation: Granted October 31, 2022

### **II. INDICATIONS FOR USE**

The RECELL Autologous Cell Harvesting Device is indicated for the treatment of thermal burn wounds and full-thickness skin defects. The RECELL Device is used by an appropriately licensed and trained healthcare professional at the patient's point of care to prepare autologous Spray-On Skin Cells for direct application to acute partial-thickness thermal burn wounds in patients 18 years of age and older, or application in combination with meshed autografting for acute full-thickness thermal burn wounds in pediatric and adult patients and full-thickness skin defects after traumatic avulsion (e.g., degloving) or surgical excision (e.g., necrotizing tissue infection) or resection (e.g., skin cancer) in patients 15 years of age and older.

### **III. CONTRAINDICATIONS**

- RECELL is contraindicated for the treatment of wounds clinically diagnosed as infected or with necrotic tissue present in wound bed.

- RECELL is contraindicated for the treatment of patients with a known hypersensitivity to trypsin or compound sodium lactate solution (Hartmann's Solution).
- The skin sample collection procedure specified for use of RECELL should not be used with patients having a known hypersensitivity to anesthetics, adrenaline/epinephrine, povidone-iodine, or chlorhexidine solutions.

#### **IV. WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the RECELL Autologous Cell Harvesting Device labeling.

#### **V. DEVICE DESCRIPTION**

The RECELL Autologous Cell Harvesting Device is a stand-alone, battery powered cell separation device operated by an appropriately-licensed healthcare professional at the patient's point of care. The device enables the processing of a small, thin split-thickness skin sample 0.006-0.008 inch (0.15-0.20 mm) in depth to prepare a cell population in suspension for immediate delivery onto a prepared wound surface. Nonclinical performance testing demonstrates processing of harvested autologous skin samples ranging in size from 1 cm<sup>2</sup> to 6 cm<sup>2</sup> using the RECELL Device generates a viable cell suspension. By processing multiple (up to 4) samples of 6 cm<sup>2</sup> autologous thin split-thickness skin, a single RECELL device can generate a volume of Spray-On Skin<sup>TM</sup> Cells sufficient to cover a treatment area of up to and including 1,920 cm<sup>2</sup>. However, as stated in the Precautions listed in the RECELL Autologous Cell Harvesting Device labeling, the RECELL Device should not be used alone for acute partial-thickness burn wounds > 320 cm<sup>2</sup> or in patients with wounds totaling >20% Total Body Surface Area (TBSA).

The device is a sterile, single use, stand-alone unit with a built-in heater, process indicators, and work surface (the RECELL Processing Unit, RPU). The user can enzymatically and mechanically process a small skin sample to produce a suspension of Spray-On Skin Cells. Processing tools provided with the device include off-the-shelf syringes, scalpels, and fill needles. The device also includes nozzles that attach to syringes and can be used to aerosolize the cell suspension onto the wound. The proprietary RECELL Enzyme is reconstituted with sterile water (included) and used to facilitate disaggregation of cells from the harvested donor skin. A buffer solution is also provided to suspend the disaggregated cells for delivery to the prepared wound site. The device is designed for point of care use. No cell culturing processes are involved in the procedure. The resulting suspension of cells comprises a mixed population predominantly of keratinocytes and fibroblasts. The presence of viable melanocytes has also been demonstrated. Additionally, sub-populations of keratinocytes critical for re-epithelialization have been identified in the Spray-On Skin Cells including basal keratinocytes, suprabasal keratinocytes, and activated keratinocytes.

The product is packaged to facilitate the processing steps for the system components,

which are provided with the RECELL RPU, and a Procedure Guide. Two configurations of the RECELL Device are available, the original RECELL Device packaging approved in the original PMA and the “ease of use” packaging configuration of the RECELL Device approved in a subsequent PMA supplement.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are several alternative approaches that may be used for the treatment of serious burns. The most common approach used for burn injuries is excision of the burn wound and prompt closure to stabilize the patient. Currently, the standard of care for wound closure is the use of autologous skin grafting. A wide variety of techniques and methods have been applied for temporary and permanent coverage of an open burn wound.

A commonly used method for reducing the amount of healthy skin harvested, i.e., autograft sparing, involves the use of an autograft meshing device that perforates the harvested skin so that it can be physically expanded and spread across a larger area. Burn surgeons frequently use an autograft, meshed at a 2:1 expansion ratio and applied to the burn injury. For patients with extensive burns, such as greater than 40% total body surface area (TBSA), use of conventional meshing ratios for autograft may not be a feasible option due to lack of sufficient donor sites.

In addition to traditional meshing techniques, other epidermal coverage strategies have been developed to decrease the amount of tissue required for harvesting, including micrografting and suction blister grafting, multiple re-harvests from donor sites, and cultured epidermal autografts. Some of these approaches fall under the purview of ‘practice of medicine’ and are not regulated by FDA; others have limited clinical data and/or are currently being studied but have not undergone complete review by the FDA.

Among the approaches considered for autograft sparing, cultured epidermal autograft products represent a commercially available autologous skin substitute offering the benefits of using autologous tissue and maximal expansion. These products have been approved for use in patients who have deep partial-thickness or full-thickness burns comprising a TBSA of greater than or equal to 30%. It must be noted that the manufacture of these types of products may involve the use of murine (mouse) cells. In these circumstances, when during the manufacturing process human cells/tissues come into immediate direct contact with live non-human cells/tissues, the FDA considers the product a xenotransplantation product. Recipients of xenotransplantation products are counseled to actively defer from donating whole blood, blood components, source plasma, source leukocytes, tissue, breast milk, ova, sperm or other body parts for use in humans due to the potential risk for transmission of a zoonotic infection acquired from mouse cells to recipients of donated fluids/tissues.

Additionally, there is no other technology available to reduce the donor area requirements for the treatment of full-thickness skin defects. There are no other point-of-care devices that allow for a 1:80 expansion for grafting in combination with more widely meshed (i.e., 3:1 meshed ratio) autografting compared to the conventional meshed (i.e., 2:1

meshed ratio) autografting. The expansion of the indication for the RECELL Device in combination with meshed autografting provides benefit by reducing donor area requirements and promoting wound closure of full thickness skin defects of different causes.

## **VII. MARKETING HISTORY**

The RECELL Autologous Cell Harvesting Device has been marketed in the United States since 2018. It has received a Conformité Européene (“European Conformity”, CE) mark and was commercialized in the European Union (EU) in 2005. Japan approval and commercialization occurred in 2022. In addition, the RECELL device also has been commercially marketed in Australia since 2006 and in China since 2008. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

Most potential adverse effects associated with the RECELL Autologous Cell Harvesting Device are those typical of care and treatment of burns and full-thickness skin defects after traumatic avulsion (e.g., degloving) or surgical excision (e.g., necrotizing soft tissue infection) or resection (e.g., skin cancer), including those related to the grafting procedure itself and subsequent wound care at both the recipient and donor sites. These include failure to heal or loss of part or all of the graft at the recipient site requiring subsequent surgical and or medical procedures, as well as edema, seroma, infection, wound decomposition, necrosis, secretion, excessive granulation tissue, rash, skin exfoliation, pain, neuralgia, scarring (hypertrophy or discoloration), blistering, folliculitis, dermatitis, erythema, pruritus, delayed healing and/or reinjury at the recipient or donor site.

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

## **IX. SUMMARY OF NONCLINICAL STUDIES**

A summary of non-clinical laboratory studies that were performed on the RECELL Autologous Cell Harvesting Device is provided below:

### **A. Laboratory Studies**

***Bench Testing – Design Verification:*** Testing was performed on discrete components and assemblies of the device to verify that individual elements function and perform as specified. The purpose and results of the design verification testing performed are summarized in Table 1 below:

Table 1 – Design Verification Testing

Test Description	Test Purpose	Results
RECELL Processing Unit (RPU) Functional Testing	Verify the integrated RPU assembly functionality met specified device requirements. The function of all features of the integrated RPU assembly was tested to established criteria as defined in the RPU specification.	Results demonstrated that all RPU assemblies passed the acceptance criteria for the self-test, run sequence, and device lock-out functionality. Temperature logs obtained during monitoring of the heating cycle of the RPU, verified that all units met the criteria and performed as specified.
RPU Environmental Use Conditions Testing	Verify the integrated RPU assembly functionality met specified device requirements at environmental operating limits.	Results of the environmental conditions testing demonstrated that all RPU assemblies passed the acceptance criteria for all functional tests at the following environmental conditions: <ul style="list-style-type: none"> <li>• Temperature: 15 - 35°C</li> <li>• Humidity: 10 – 90% relative humidity (RH)</li> <li>• Pressure: 65 – 106 kPa</li> </ul>
Spray Nozzle – Cell Distribution	Demonstrate the cell distribution obtained using the RECELL device spray nozzle provides sufficient coverage during application.	Sprayed cell suspensions demonstrated adequate coverage. The results indicate that the sprayed cells are spread over the surface and provide coverage over nearly the entire surface.
Enzyme Activity Verification	Verify that the reconstituted Enzyme maintained sufficient activity to make viable cell suspensions when processing multiple skin samples.	Results show the enzyme activity remained above the acceptance criterion for all test groups throughout the processing cycle. Use of the same Enzyme solution for multiple samples did not significantly impact cell disaggregation or viability of the cells.

***Bench Testing – Integrated Device Performance:*** Testing was performed using complete RECELL devices to establish that the different steps of tissue processing with the device are capable of reproducibly processing tissue into viable cell suspensions. The conditions and methods were planned to simulate the intended skin sample processing procedure for the RECELL Device. The objective was to characterize and demonstrate the technical capability of the integrated device under controlled simulated conditions. The purpose and results of the design verification testing performed is summarized in Table 2 below:

Table 2 – Integrated Device Performance Testing

Test Description	Test Purpose	Results
Cell Suspension Characterization	To establish cell processing yields, to verify the viability of cells pre- and post-spray application, and to determine the proportion of cell types. The study also evaluated the	<p>The following results were observed:</p> <ul style="list-style-type: none"> <li>• Verified that no significant differences in cell viability occurred between pre- and post-spray suspensions produced by the RECELL Device, nor between small and large skin graft sizes.</li> </ul>
Cell Suspension Characterization (cont.)	cell suspension for the proportion of single cells to aggregates and to confirm that the tissue processing did not significantly increase apoptotic activity. The intent of this study was to demonstrate the ability of the device to produce viable cell suspensions.	<ul style="list-style-type: none"> <li>• Results demonstrated that fibroblasts and keratinocytes represent the largest proportions of cells, followed by a small proportion of melanocytes.</li> <li>• Determined the absence of cell aggregates of any size in amounts of significance that could affect the application of cell suspensions to patient wounds.</li> <li>• Only approximately 2% of cells in the suspension were apoptotic, and verified that pre- and post-spray suspensions did not have statistically different apoptotic activity.</li> </ul>
Cell Suspension Reproducibility	Establish that when used by different operators the RECELL Device can generate viable cell yields similar to or greater than yields established in the cell characterization study.	In all cases, users were able to prepare suspensions with viable cell yields at the average or above cell yields established in the cell suspension characterization study. This confirmed that different users could consistently process tissue samples using the RECELL Device to produce cell suspension with viable cells.
Enzyme Carry-Over Testing	Confirm that there is a significant decrease in (b) (4) in the final cell suspension	It was observed that even without (b) (4) in the (b) (4), the enzyme carry-over based on (b) (4) was minimal. With immersion in (b) (4), the average carry-over dropped slightly further than without (b) (4).

**Biocompatibility:** Biocompatibility testing was performed on the sterile RPU assembly, spray nozzles and Enzyme. Testing was performed by an independent testing facility on finished and sterilized product in accordance with International Organization for Standardization (ISO) 10993-1:2009 “*Biological Evaluation of Medical Devices Part-1: Evaluation and Testing*” as specified in the FDA guidance ‘*Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and testing within a risk management process*’ dated June 16, 2016.

Biocompatibility tests were conducted in compliance with U.S. Food and Drug Administration Good Laboratory Practice (GLP) regulations set forth in 21 CFR Part 58. All biocompatibility tests passed their corresponding acceptance criteria. Table 3 and Table 4 summarize the results of biocompatibility tests that were performed.

Table 3 – Biocompatibility Testing for RPU Assembly and Spray Nozzles

<b>Biocompatibility Test</b>	<b>Results</b>	<b>PASS/FAIL</b>
Cytotoxicity	Non-Cytotoxic	PASS
Guinea Pig Maximization Sensitization Test	No evidence of sensitization	PASS
Intracutaneous Reactivity Test	Non-irritant	PASS
Acute Systemic Injection Test	Non-Toxic	PASS
Rabbit Pyrogen Test (Material Mediated)	Non-pyrogenic	PASS

Table 4 – Biocompatibility Testing for Enzyme

<b>Biocompatibility Test</b>	<b>Results</b>	<b>PASS/FAIL</b>
Genotoxicity: <i>Salmonella typhimurium</i> Reverse Mutation Assay – Ames Test	Non-mutagenic	PASS
Genotoxicity: In Vitro Mouse Lymphoma Assay	Non-mutagenic and non-clastogenic	PASS
Genotoxicity: In Vivo Mouse Micronucleus Assay	Non-mutagenic	PASS



***Sterility Assurance:*** The applicable components and assemblies of the RECELL Device are sterilized by the following traditional methods:

- Enzyme: Gamma radiation sterilization cycle;
- Buffer: Moist heat sterilization;
- RPU: Ethylene Oxide gas sterilization;
- Spray Nozzle Assembly: Gamma radiation sterilization cycle.

For the Enzyme and the spray nozzle assembly, sterilization validations were completed in accordance with the following standards:

- ISO (b) (4)

- ISO (b) (4)

A Verification Dose Maximum (VD<sub>max</sub>) method was used for the substantiation of the gamma radiation sterilization dose. All required testing as established by the above standards for sterilization validation was successfully performed and passed all acceptance criteria. The gamma sterilization dose has been successfully demonstrated to be effective in providing the sterility assurance level (SAL) of (b) (4) for the Enzyme and spray nozzle assembly of the RECELL Device.

For the Buffer, a sterilization validation was completed in accordance with ISO (b) (4)

. An (b) (4) validation method was employed to assure an SAL (b) (4). All required testing as established by the above standard for moist heat sterilization validation was successfully performed and passed all acceptance criteria.

For the RPU, a sterilization validation was completed in accordance with ISO (b) (4)

. An (b) (4) validation method was employed to assure an SAL (b) (4). All required testing as established by the above standard for ethylene oxide sterilization validation was successfully performed and PASSED all acceptance criteria.

Representative samples of the RPU were evaluated for Ethylene Oxide and (b) (4)

. Based on the results, ethylene oxide (b) (4) for the RPU were within specified limits for limited exposure (b) (4)

**Packaging Integrity / Shipping Testing:** The RECELL Device is packaged in a single corrugated shelf box that has a sliding inner tray that contains a single sterile-packaged RPU and three (3) component set boxes. The capability of the device packaging to protect the device and maintain a sterile barrier has been validated in accordance with the following standards:

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

Applicable RECELL components were subjected to the following worst-case sterilization conditions prior to conditioning:

- Enzyme and Nozzles- Gamma radiation: Maximum dose (b) (4)
- Buffer- Moist heat: (b) (4) steam cycle
- RPU- EO: (b) (4) ethylene oxide cycle

Finished packaged RECELL devices were subjected to the following conditioning prior to testing:

- Environmental conditioning (b) (4)
- Simulated transportation conditioning (in accordance with ASTM (b) (4))

Results of the device and package integrity testing demonstrate that all components of the RECELL Device met all defined acceptance criteria after being subjected to the environmental and shipping conditions. The integrity of all sterile barrier packages was demonstrated to be intact with (b) (4) detected and the seal strength was maintained within specification for all packages. Container closure integrity for all vials of Enzyme, Buffer, and water-for-injection (WFI) were demonstrated to remain intact with (b) (4) within the specified limits. All remaining tests for product integrity and functionality demonstrated that all components were unaffected by the conditioning and met their design specifications. The packaging configuration of the RECELL Device was qualified to provide a sterile barrier and sufficient protection for the device under expected storage, handling and distribution conditions.

**Shelf Life of RECELL device:** Product stability and sterile package shelf life are being qualified under an on-going stability test program. Finished packaged RECELL devices were initially subjected to the following conditioning prior to testing:

- Sterilization:
  - Enzyme and Nozzles- Gamma radiation: Maximum dose (b) (4)
  - Buffer- Moist heat: (b) (4) steam cycle
  - RPU- EO: (b) (4) ethylene oxide cycle
- Environmental conditioning (b) (4)
- Simulated transportation conditioning (in accordance with ASTM (b) (4))

RECELL devices were subjected to real-time aging at ambient conditions (25°C/60% RH). To substantiate shelf-life, real-time aging was performed from 3 months to the final shelf-life duration. At each time point the product integrity and functionality testing is performed.

Currently, product stability and packaging shelf life at 3, 6, 12, 18, (b) (4) months real-time for the RECELL Device components (without Enzyme) have been completed. Results of testing demonstrate that the components of the RECELL Device met all defined acceptance criteria for product stability and package integrity after being subjected to the aging conditions.

It is noted that the Enzyme stability is evaluated separately. The finished and packaged Enzyme component will be subjected to the following conditioning prior to testing:

- Sterilization - Gamma radiation: Maximum dose (b) (4)
- Environmental conditioning (b) (4)
- Simulated transportation conditioning (in accordance with ASTM (b) (4))

Real time aging was performed from 3 months under ambient temperature 25°C and 60% RH. At each time point the product stability and container integrity testing was performed. Determining stability of the RECELL Enzyme device component included measurement of the Enzyme's activity using a (b) (4) -based assay that has undergone prior validation.

A retrospective study of Enzyme stability has been performed using Enzyme samples stored at 20-25°C. Results from the retrospective study provide sufficient initial evidence to support a 6-month shelf life for the RECELL Device (based on available stability data provided for the activity of the Enzyme component). A

prospective study assessing Enzyme stability was performed to support extension of the original shelf-life to (b) (4) months.

**Electromagnetic Compatibility and Electrical Safety Testing:** Electromagnetic Compatibility (EMC) testing was performed on a standalone RPU of the RECELL Device. Testing included compliance for both emission and immunity tests in accordance with (b) (4). The RPU assembly of the RECELL Device met all the applicable requirements of (b) (4).

Electrical safety testing of the RECELL device was performed in accordance with (b) (4).

In addition, safety testing performed in accordance with (b) (4) for usability of the RECELL device. Overall testing results demonstrate the RECELL meets all applicable requirements set forth in (b) (4).

**Software Testing:** Testing was conducted to ensure the performance of the embedded RPU firmware (the only software containing component of the RECELL Device) met the software requirements specifications. Verification and validation activities were completed for the device firmware according to the FDA guidance ‘*General Principles of Software Validation*’ dated January 11, 2002. Testing of the firmware implementation was accomplished through unit, integrated system, and regression testing. The results of all software testing passed all test criteria and based on these results the RECELL Device firmware was verified and validated to meet its functional requirements.

**Human Factors and Usability:** The Human Factors Report provided in the PMA original submission contains summative validation results which demonstrate the RECELL Device user interface (including the device and accessories, Instructions for Use (IFU), Procedure Guide (PG), and representative training) allows for safe and effective operation for the intended use by intended users within the intended environment, without compromise to medical care or patient or user safety. The Report was in alignment with FDA/Center for Devices and Radiologic Health (CDRH) Human Factors guidance and FDA-recognized Human Factors standards:

- FDA CDRH's final guidance: Applying Human Factors and Usability Engineering to Medical Devices that was issued on February 3, 2016
- IEC 62366-1:2015, titled Medical Devices – Part 1: Application of Usability Engineering to Medical Devices
- AAMI/ANSI HE75: 2009 Human Factors Engineering – Design of Medical Devices

The summative validation study was performed with a total of (b) (4) healthcare professionals who specialized or were experienced in burn care and with intended prior experience with aseptic technique. Each participant completed a series of simulated use scenarios in a representative operating room as they were observed and asked questions by independent moderators. During the collection of objective and subjective data, it was found that all users were able to prepare and apply a simulated cell suspension successfully. No user errors were observed that would lead to or result in death or a severe or permanent injury to the patient or user. There were no critical user errors that would be further mitigated via modifications of the device or user interface and therefore the device has been demonstrated to be suitably designed for its intended use.

## **B. Animal Studies**

Three animal studies were conducted during the initial development of the RECELL Device to establish feasibility of applying autologous cell suspensions to a wound bed. The first two studies were performed early in the development life cycle of the RECELL Device to focus on the feasibility and potential of using an autologous cell suspension to improve wound healing with split thickness autografts. These studies occurred prior to completion of the finished device but used a similar process to the current RECELL Device to generate and apply a cell suspension. A third study was performed using Spray-On Skin Cells from the RECELL Device in combination with a skin substitute. Each of these three studies were designed to evaluate the ability of a cell suspension to facilitate wound re-epithelialization. All three studies were performed in a porcine model, as this has been identified as an acceptable wound healing model. These studies demonstrated that use of an autologous cell suspension combined with autograft for full-thickness wounds can reduce the time required for wound re-epithelialization when compared to autograft alone. FDA has reviewed the findings in these publications and found them supportive of this approach for human studies.

## **C. Additional Studies**

***Viral Clearance Studies:*** The RECELL Device uses an animal-derived enzyme as the active ingredient of the RECELL Enzyme in the cell suspension preparation process.

To establish that the RECELL Enzyme poses a minimal risk of introducing adventitious viruses to a patient, a study based on peer-reviewed literature and expert interpretation has been performed to evaluate the risk control measures used to ensure adequate viral inactivation. A risk-based approach that combines the recommendations from the FDA draft guidance ‘Medical Devices Containing Materials Derived from Animal Sources’ dated January 23, 2014 with another regulatory guidance concerning the use of animal-derived enzyme in the manufacture of human biological medicinal products (EMA/CHMP/BWP/814397, effective September 1, 2014) was employed to evaluate the manufacturing process and procedural steps that facilitate viral inactivation.

Worst-case estimates of potential viral contamination of the most difficult viruses showed higher than a (b) (4), consistent with expectations set forth in the FDA draft guidance.

The effectiveness of the current control measures has been verified for viral clearance in the manufacture of the Enzyme of the RECELL Device.

***Bacterial Endotoxin Testing:*** Routine bacterial endotoxin testing (BET) is performed on every lot of the device. Testing was conducted in accordance with the recommendations described in Section V part A.4 of the FDA Guidance “*Submission and Review of Sterility Information in Premarket Notification (510(k) Submissions for Devices Labeled as Sterile*” issued on January 21, 2016 to support this labeling. Due to the number of separate sterile components provided as part of the RECELL Device, routine testing is performed on separate components and then the total sum of endotoxin levels from all applicable components is used to determine if the lot has met the BET release criteria. The total combined endotoxin exposure attributable to all device components was demonstrated to be (b) (4) after considering a worst-case enzyme carryover scenario involving the final disaggregated skin cell suspension device output. (b) (4) test methods per (b) (4) are used to detect and quantify bacterial endotoxin for all applicable components of the RECELL Device, with an exception made for the RECELL Enzyme which requires using a modified validated method for sample preparation followed by testing in accordance with (b) (4).

## **X. SUMMARY OF PRIMARY CLINICAL STUDIES AND EXPANDED ACCESS DATA**

Two prospective randomized clinical studies, CTP001-5 and CTP001-6, were conducted under BB-IDE 13053 to evaluate the safety and effectiveness of the RECELL Device in the treatment of acute burn wounds in a total of 131 subjects.

One prospective randomized clinical study, CTP007, was conducted under BB-IDE 13053 to evaluate the safety and effectiveness of the RECELL Device in the treatment of non-thermal full-thickness skin defects in a total of 65 subjects.

Collectively, these studies evaluated wound closure results with RECELL compared to conventional autografting, as well as the differences in donor skin requirements between the two approaches. In addition to healing, short-term outcomes such as pain, infection and graft loss were also evaluated. Long-term outcomes included evaluation of durability

of healing, scarring and patient satisfaction. Study design, study subject demographics, safety and effectiveness endpoints for the three studies are summarized below.

Further, retrospective analyses were conducted on data from 39 pediatric patients with acute full-thickness thermal burn wounds, who received the RECELL Device in Expanded Access and Continued Access protocols (Studies CTP004 and CTP001-8), 49 patients 18 years of age and older with >50% TBSA acute full-thickness thermal burn wounds, who received the RECELL Device in Expanded Access (Study CTP004), and 61 patients with acute full-thickness burn wounds over a joint (including hands) in the expanded access (CTP004).

Together, the clinical outcomes support the use of the RECELL Device for treatment of thermal burn wounds and non-thermal full-thickness skin defects. The RECELL Device can be used in combination with meshed autografting to reduce the donor area requirements and promote wound closure of full-thickness thermal burns and full-thickness non-thermal skin defects. The RECELL Device can also be used alone to promote wound closure of deep partial-thickness thermal burns.

## **A. Study Design**

### **Study CTP001-6:**

In this randomized, multi-center, standard-of-care controlled study, RECELL was used in combination with autografts that had a higher meshing ratio than control, for the treatment of deep (including full-thickness), extensive burn injuries. The study population included 30 subjects from 6 clinical sites. Subjects were older than 5 years with 5-50% TBSA burn injuries requiring autografts for closure. Each subject served as their own control, using two comparable contiguous or non-contiguous areas of at least 300 cm<sup>2</sup> in size. The areas were randomly assigned to receive autografting consistent with the investigator's pre-specified graft plan (control) or application of the Spray-On Skin Cells over autograft meshed more widely (one ratio higher) than identified in the pre-specified graft plan.

Acute healing and pain outcomes were evaluated through 12 weeks; and pain, healing, durability, and scar outcomes were evaluated in the longer-term follow-up visits conducted at 24, 36, and 52 weeks.

#### **1. Clinical Inclusion and Exclusion Criteria**

Enrollment was limited to subjects who were at least five years of age with an acute thermal burn injury of 5-50% total body surface area (TBSA) requiring skin grafting with two areas at least 300 cm<sup>2</sup>, excluding hands, face and joints. Patients were not permitted to enroll in this study if their burn wounds were due to chemical, electrical, or radioactive sources.

#### **2. Follow-up**

Schedule:

All patients were scheduled to return for follow-up examinations at Week 1

+/- 1 day, Week 2 +/- 3 days, Week 4 +/- 3 days, Week 6 +/- 3 days, Week 8 +/- 5 days, Week 10 +/- 5 days, Week 12 +/- 5 days, Week 24 +/- 14 days, Week 36 +/- 14 days, and Week 52 +/- 28 days postoperatively.

**Assessments:**

Preoperative digital photographs of the Control and RECELL treated wound sites and the donor autograft sites were taken. Postoperative assessments included the following: 1) Visual Analog Scale (VAS) of study subjects' satisfaction of the appearance of the donor, control, and RECELL sites at all time points and 2) blinded evaluator, and study subject completion of the Patient and Observer Scar Assessment Scale (POSAS) to assess the characteristics of the wound scar at 12, 36, and 52 weeks. Clinical assessments were performed at all time points. Adverse events and complications were recorded at all visits.

**3. Clinical Endpoints**

The co-primary study endpoints were: 1) Non-inferiority (pre-specified non-inferiority margin of 10%) of the incidence of complete wound closure of burn injuries treated with the combination of Spray-On Skin Cells and more widely meshed autografts compared to that for Control (conventional autograft) wounds at eight weeks post-treatment, as assessed by a blinded evaluator; and 2) Superiority in reduced donor area autograft requirements for RECELL versus control treatment (to establish RECELL as an autograft-sparing technology), as assessed by the Geometric Mean Ratio (GMR) of the RECELL:Control autograft expansion ratios, at the time of the autograft procedure. Complete wound closure was defined as complete skin re-epithelialization without drainage, confirmed at two consecutive study visits at least two weeks apart. Safety assessment included evaluation of healing time based on the investigator's assessment, infection, allergic response to trypsin, durability of wound-healing, scarring outcomes, and device-related adverse events and serious adverse events.

Regarding safety, delayed wound healing, infection and graft failure were adverse events of particular interest.

Regarding effectiveness, subject satisfaction and pain scores were of additional interest.

Regarding success/failure criteria, confirmed complete wound closure prior to eight weeks was defined as treatment success, with the pre-specified non-inferiority margin of 10% (Control minus RECELL) constituting study success. The other success criterion (co-primary effectiveness outcome) was superiority of RECELL at the donor site, relative to Control, based on reduction in amount of harvested donor skin.

**Study CTP001-5:**

In Study CTP001-5, the RECELL Device was evaluated as a primary intervention for the treatment of acute burn injuries in a randomized, multi-center, standard of care



controlled (standard split-thickness meshed skin graft) study. The study population included consenting subjects between the ages of 18 and 65 with 1-20% TBSA thermal burn injuries. Each subject served as his/her own control, using two comparable contiguous or non-contiguous areas of deep partial-thickness burns. One site was treated with Spray-On Skin Cells produced by RECELL, and the other was treated with 2:1 meshed autograft. Subjects were evaluated at 1, 2, 3, 4, 8, 16, 24, and 52 weeks.

1. Clinical Inclusion and Exclusion Criteria

Enrollment was limited to subjects who had acute thermal burn injuries requiring skin grafting for closure (deep, partial-thickness) over 1-20% TBSA and who were 18-65 years of age. Subjects were not permitted to enroll in the study if their burn wounds were due to chemical, electrical, or radioactive sources.

2. Follow-up

Schedule:

All patients were scheduled to return for follow-up examinations at 1, 2, 4, 6, 8, 10, 12, 24, 36, and 52 weeks after treatment.

Assessments:

Preoperative digital photographs of the Control and RECELL -treated wound sites and the donor autograft sites were taken. Postoperative assessments included the following: Visual Analog Scale (VAS) of study subjects' satisfaction of the appearance of the donor, control, and RECELL sites at all time points; also, the Vancouver Scar Scale (VSS) was evaluated starting at Week 16. Clinical assessments were performed at all time points. Adverse events and complications were recorded at all visits.

The key time points are shown in Table 5 which provides a summary of the study design and safety and effectiveness endpoints.

Table 5 – Study Design and Safety and Effectiveness Endpoints

<b>Study</b>	<b>A Comparative Study of RECELL Device and Autologous Split-thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries (Deep Partial-Thickness Burns) – CTP001-5</b>	<b>Demonstration of the Safety and Effectiveness of RECELL combined with Meshed Skin Graft for Reduction of Donor Area in the Treatment of Acute Burn Injuries (Mixed Depth Burns) – CTP001-6</b>
<b>Multi-Center</b>	12 US Institutions	6 US Institutions
<b>Randomized</b>	101 subjects	30 subjects
<b>Controlled</b>	Within-subject control	Within-subject control

<b>Study</b>	<b>A Comparative Study of RECELL Device and Autologous Split-thickness Meshed Skin Graft in the Treatment of Acute Burn Injuries (Deep Partial-Thickness Burns) – CTP001-5</b>	<b>Demonstration of the Safety and Effectiveness of RECELL combined with Meshed Skin Graft for Reduction of Donor Area in the Treatment of Acute Burn Injuries (Mixed Depth Burns) – CTP001-6</b>
<b>Burns treated</b>	Acute thermal burn injuries requiring skin grafting for closure (deep partial-thickness)	Acute mixed depth (deep partial-thickness and full-thickness) thermal burn injuries requiring skin grafting for closure
<b>Burn % TBSA</b>	1-2	5-50
<b>Subjects Age</b>	18-65	≥5
<b>Control Treatments</b>	2:1 meshed standard autograft	Conventional autograft (sheet or meshed)
<b>RECELL Treatment</b>	Spray-On Skin Cells applied directly to prepared wound bed	Spray-On Skin Cells applied over autografts meshed more widely (one ratio higher) than pre-specified conventional autograft comparator
<b>Co-Primary Effectiveness Endpoints: Donor Site</b>	Incidence of healing at 1 week <i>Defined as 100% epithelialization with a contiguous layer of viable epithelium confirmed at two consecutive study visits</i>	Relative reduction in donor area requirements
<b>Secondary Effectiveness Endpoints</b>	Epithelialization at each visit, recipient site wound closure at week 2, and subject assessment of pain (week 1-week 8) and appearance (week 16-week 52)	Patient satisfaction between treatment sites, overall observer opinion POSAS score, and overall patient opinion scores (24 weeks)
<b>Safety Endpoints</b>	Adverse events, graft loss, infection, scar formation, delayed healing /wound assessment, and allergic response to trypsin	Adverse events, delayed healing, infection, long-term durability, allergic response to trypsin, pain, and scarring necessitating surgical intervention
<b>Follow-Up Schedule</b>	Follow-up visits at 1, 2, 3, 4, 8, 16, 24, and 52 weeks after treatment.	Follow-up visits at 1, 2, 4, 6, 8, 10, 12, 24, 36, and 52 weeks after treatment.

### 3. Clinical Endpoints

The co-primary effectiveness endpoints were: 1) Non-inferiority of the incidence of RECELL recipient site (burn injury) wound closure ( $\geq 95\%$  re-epithelialization) at 4 weeks compared to that of the Control. The pre-specified non-inferiority margin was  $-10\%$  (RECELL minus Control); and 2) Superiority of the incidence of donor site healing at 1 week (100% re-epithelialization) for the RECELL donor site compared to that of the Control site. For both endpoints, healing was confirmed at two consecutive visits. Safety assessments included evaluation of delayed healing, infection, allergic response to trypsin, wound durability, scarring outcomes, device-related adverse events and serious adverse events.

Regarding safety, delayed wound healing, wound scarring, infection and graft failure were adverse events of particular interest.

Regarding effectiveness, patient satisfaction and pain scores were of additional interest.

Regarding success/failure criteria, confirmed complete wound closure prior to four weeks was defined as treatment success, with the non-inferiority of RECELL relative to Control constituting study success. The other success criterion (co-primary effectiveness outcome) was superiority of RECELL at the donor site, relative to Control, based on complete donor site healing at one week.

#### **Study CTP007**

This is a prospective, multicenter, intra-subject randomized and controlled, evaluator-blinded study to compare the clinical performance of conventional meshed autografting versus more widely meshed autografting plus Spray-On Skin Cells prepared using the RECELL Device on nonburn full-thickness skin defects of various etiologies.

Each subject contributed two comparable wound areas, which were either two separate areas or one contiguous area divided in two. The two comparable wound areas were required to be similar in size (within  $\pm 20\%$ ), severity of injury, and prior treatment. The two comparable wound areas were randomized at 1:1 ratio to receive either the prespecified conventional meshed autografting (i.e., 2:1 meshed ratio) alone (control-treated area) or more widely meshed autografting (i.e., 3:1 meshed ratio) plus Spray-On Skin Cells prepared using the RECELL Device (RECELL-treated area). Based on investigator discretion, the Spray-On Skin Cells could also be applied to the donor site(s).

The RECELL-treated areas and the control-treated areas were compared with respect to wound closure and donor skin requirements. Subjects were evaluated over a period of 26 weeks.

#### 1. Clinical Inclusion and Exclusion Criteria

Eligible subjects were at least five years of age who required autografting for

treatment of nonburn full-thickness skin defects (e.g., trauma- or surgery- related injury) with a maximum of 50% total body surface area (TBSA) requiring skin grafting with each area at least 80 cm<sup>2</sup> (or 160 cm<sup>2</sup> contiguous), excluding face and genitalia. Patients were excluded in this study if they had conditions and medications that the investigator determined could compromise subject safety or study objectives, known hypersensitivity to trypsin or compound sodium lactate for irrigation (Hartmann's) solution, or a life expectancy of at least 1 year.

## 2. Follow-up schedule:

All subjects were scheduled for follow-up examinations at 1, 2, 4, 6, 8, 10, 12, and 26 weeks after treatment.

### Assessments:

Efficacy was evaluated based on the coprimary endpoints: a noninferiority test for wound closure at (or prior to) 8 weeks post-treatment, and a superiority test for the ratio (RECELL to control) of actual expansion ratios (i.e., RECELL-treated area/corresponding donor area to control-treated area/corresponding donor area).

At all visits, all subjects' study treatment areas were documented photographically using standardized digital photography.

Safety assessment included reporting treatment emergent adverse events (TEAEs).

## 3. Clinical Endpoints

The co-primary study endpoints were: 1) Non-inferiority (pre-specified non-inferiority margin of 10%) of the proportion of complete wound closure of RECELL-treated areas and control-treated areas by (or prior to) Week 8, confirmed at two consecutive study visits at least 2 weeks apart, assessed by a blinded evaluator, in the Per-Protocol (PP) population; 2) Superiority in reduced donor area autograft requirements for RECELL versus control treatment, as the ratio of actual expansion ratios, defined as the ratio (RECELL to control) of the measured treatment area (size) to the measured donor skin area (i.e., RECELL-treated area/corresponding donor area to control-treated area/corresponding donor area, including donor skin needed for secondary treatments) in the intent-to-treat (ITT) population.

### **Retrospective Reviews:**

- I. Two retrospective reviews were conducted to evaluate the safety and effectiveness of RECELL with meshed autograft for the treatment of full-thickness burns, utilizing data collected in patients who received RECELL combined with meshed autograft in Expanded Access and Continued Access protocols (RECELL Cohort).

The RECELL Cohort data were compared with data from patients in the American Burn Association's National Burn Repository (NBR Control), who received standard of care (conventional autograft). Week 8 wound healing data (not available in the NBR) were reported for the RECELL Cohort. RECELL Cohort adverse events were compared with the adverse events in the randomized controlled trial (RCT Cohort). Propensity score (PS) stratification was used to reduce bias attributable to potential differences in key covariates such as age, sex, %TBSA and Baux Score, between RECELL and NBR Control datasets.

### Clinical Endpoints

The primary endpoint was the number of autograft treatments required to achieve definitive closure per patient, comparing the RECELL Cohort to the NBR Control. Difference in length of hospital stay (LOS) between the RECELL Cohort and NBR Control was a secondary endpoint. LOS was measured as:

$$\text{Days per \%TBSA} = \frac{\text{Number of inpatients hospital days}}{\text{Burn injury size (\%total body surface area)}}$$

Safety assessments included mortality in RECELL Cohort compared with NBR Control, specified adverse events (infections, skin graft failure, graft loss and/or impaired healing, compared to the RCT Control), and wound durability (no comparison).

- II. Another retrospective analysis of the available data from an expanded access (CTP004) was conducted to evaluate the safety and efficacy of RECELL combined with meshed autograft for the treatment of full-thickness burns over joints and hands.

### Clinical Endpoints

In the retrospective analysis, the primary endpoint was defined as the proportion of RECELL-treated areas (joint/hand vs. non-joint) closed by Week 8.

## **B. Accountability of PMA Cohort**

### Study CTP001-6

Thirty subjects were enrolled. All 30 of these comprise the safety population, and 26 were included in the Per-Protocol analysis of the primary non-inferiority effectiveness endpoint. Four of the enrolled 30 subjects were excluded from analyses due to major protocol deviations (two subjects missed the primary endpoint visit at week eight and two study subjects' wounds included a joint, in violation of the enrollment criteria). The intention to treat (ITT) population for the assessment of superiority at the donor site consisted of 29 subjects.

#### Study CTP001-5

Of the 101 subjects enrolled in this study, 83 were available for assessment of the primary non-inferiority effectiveness evaluation (the modified Per-Protocol population), and 100 were available for evaluation of superiority at the donor site (the ITT population).

#### Study CTP007

The ITT population included 65 subjects whose treatment areas were randomized and received the treatments. The PP population included 52 subjects who received both treatments and did not have any major protocol deviations.

### **C. Study Population Demographics and Baseline Parameters**

#### Study CTP001-6

Thirty subjects were enrolled in the study, and their wound sites were randomized to the control or the treatment group. The majority of subjects were male (25/30, 83.3%); 66.7% were Caucasian (20/30). The mean age was 39.1 years. Nine subjects had risk factors for impaired wound healing including smoking, drug and alcohol abuse, and inadequate nutrition. The majority of the burn injuries were the result of fire or flames (22/30, 73.3%). The mean percent TBSA affected by burn injuries was 21.2% ( $\pm 12.8\%$ ).

#### Study CTP001-5

A total of 101 subjects enrolled in the study at 12 US Centers. The mean age of the subjects was 39.5-years (range: 18.2- 63.5), with the majority being male (85/101, 84.2%) and Caucasian (59/101, 58.4%). Most of the burn injuries were the result of fire or flames (78/101, 77.2%). Mean percent TBSA affected by burn injuries was 10% ( $\pm 4.53\%$ ) with similar autografting areas for RECELL and Control recipient (treatment) sites ( $168.2 \pm 68.0 \text{ cm}^2$  vs.  $165.0 \text{ cm}^2 \pm 66.5 \text{ cm}^2$ , respectively;  $p=0.3656$ ). On average, autografting was performed 7 days following the burn injury, demonstrating that these partial-thickness burns failed to heal with conservative measures, and therefore confirming that autografting was indicated.

#### Study CTP007

Sixty-five patients with a mean age of 45.7 years (range 15-85 years) from 18 clinical sites were enrolled. Majority of subjects were male (44/65, 67.7%) and white (71%). The types of wounds included acute and chronic wounds of necrotizing (35.4%) and other (9.2%) infections, open (16.9%) and closed (6.2%) degloving injuries, fasciotomy/compartment Syndrome (7.7%), surgical (7.7%), crush injury (4.6%), traumatic hematoma (3.1%), flap donor (3.1%),

road rash (3.1%), gunshot wound (1.5%) and laceration wound (1.5%). The median size of RECELL-treated and the control-treated areas were 160 cm<sup>2</sup> (ranged 80 to 1155 cm<sup>2</sup>) and 156 cm<sup>2</sup> (ranged 80 to 1155 cm<sup>2</sup>), respectively, and the wounds were located at arms, legs, back, buttocks, and anterior-torso. The mean affected area was 5.0% ( $\pm$ 3.9%) of TBSA.

#### Retrospective Review of Patients $\geq$ 18 Years of Age with $>$ 50% TBSA Acute Full-thickness Thermal Injury

Data from 49 patients with 342 mixed-depth acute thermal burn wounds treated under Expanded Access (Study CTP004) with RECELL combined with meshed autograft were included within the RECELL Cohort. Data from 277 patients were included in the NBR Control, and 28 patients were included in the RCT Control. The RECELL Cohort and NBR Control had comparable baseline characteristics regarding age, sex, %TBSA and Baux scores. Percent TBSA and Baux scores were greater for the RECELL Cohort compared with the RCT Control.

#### Retrospective Review of Patients $<$ 18 Years of Age with Acute Full-thickness Thermal Injury

In the RECELL Cohort, 39 pediatric patients (mean age of 7.1 years) with 175 acute thermal burn wounds were treated, under Expanded Access (Study CTP004) or Continued Access (Study CTP001-8), with RECELL in combination with meshed autografts. In the NBR Control, 245 pediatric patients (mean age of 8.7 years) were treated with conventional autografts. Mean total estimated injury size (%TBSA) was greater in the pediatric RECELL Cohort (40.1%) compared with the NBR Control (28.1%). Other demographics including age, sex, and Baux scores were comparable between the two groups.

#### Retrospective Analysis of Patients with Full Thickness Thermal Injuries over Joints and Hands

The analysis included 61 patients treated under expanded access (CTP004), who had wound closure data available on 443 RECELL-treated areas (237 areas contained a joint including hand [experiment areas] and 206 areas did not involve a joint or hand [control areas]) at Week 8. The patients' mean age was 31.4 years (range 1.2-68.9 years). Majority of patients were male (37/61, 60.7%) and White (37/61, 60.7%). Almost all the injuries were burn wounds (60/61, 98.4%). The mean affected area was 54.1% ( $\pm$ 15.5%) of total body surface area (TBSA). Only about 50% of the wounds had the wound size measurements available (122/237 in areas involving joints/hands and 117/206 areas not involving joints/hands).

### **D. Safety and Effectiveness Results**

## 1. Safety Results

### Study CTP001-6

No unanticipated adverse device effects or device-related events were reported. The number of subjects with any treatment-emergent adverse event (TEAE) at the RECELL treatment site was the same as the number of subjects with any TEAE at the Control treatment area (17/30, 57%).

Similar numbers of TEAEs were reported in areas that were not involved in the study treatments (63%), and 17% of reported TEAEs were not related to any burn. Most subjects experienced TEAEs that were mild (27%) or moderate (37%). There was no overt difference between RECELL and Control in the incidence of TEAEs at the treatment area (impaired healing, pain, graft loss, skin abrasion, and skin graft failure). The most common TEAE at both the RECELL and Control treatment areas was pruritus, experienced by 7 (23%) subjects. One or more severe TEAEs were experienced by 7 (23%) subjects; however, no TEAE were related to the RECELL device. Twelve subjects had serious adverse events (SAEs), and one died as a result of the SAEs (acute respiratory distress syndrome and subarachnoid hemorrhage, both of which were severe and not related to the study device). There was no difference in the incidence and types of SAEs at the RECELL and Control treatment areas.

### Study CTP001-5

Of the 101-subjects, 58% experienced an adverse event, with 36% having an adverse event at the RECELL sites and 23% at the Control sites.

Overall, adverse experiences reported for RECELL-treated sites were typical for the type of injury sustained by subjects with burn wounds requiring skin grafting procedures. A greater number of subjects had adverse events at the RECELL sites when compared with the Control sites; however, most of these events were mild in nature, were not considered device-related, and were not serious.

Additionally, the greater incidence of adverse events noted at RECELL recipient sites is primarily attributed to events including events contributing to primary endpoint failures, re-injury at the recipient site, and other primarily self-limited skin and subcutaneous tissue disorders such as blisters and excessive granulation tissue. There was no overt difference in the incidence of adverse events between the RECELL or Control donor sites (4.0% vs. 6.9%, respectively). The observed systemic AEs are consistent with a study population undergoing grafting, and there is no evidence of systemic toxicity associated with the application of Spray-On Skin Cells. In ancillary burn injury areas not included in the randomized treatment areas, 27.7% of subjects experienced similar AEs to the study sites including hypertrophy, hypertrophic scarring, and additional injury (i.e., laceration, skin wound, and skin injury).

### Study CTP007



The safety population included 65 subjects who were randomized and received treatment. The systemic safety evaluation was confounded due to the intra-subject randomization and control of the treatment areas; however, the systemic effect is unlikely due to topical route of administration of Spray-On Skin Cells.

Among the 65 subjects, 48 (73.8%) subjects had a total of 198 treatment-emergent adverse events (TEAEs). Forty-two (64.6%) subjects had 158 nonserious TEAEs, and 19 (29.2%) subjects had 40 serious adverse events (SAEs).

All the SAEs, including the three fatal SAEs, were considered unlikely related to the study procedure or the RECELL treatment. The study population was in significant physical distress. Subjects enrolled in this study required either long-term hospitalization or frequent admissions for surgical and medical managements. The SAEs were probably related either to the large cutaneous wounds and their complications or the subjects' underlying comorbidities.

The risks of the RECELL Device in combination with meshed autografting for the treatment of full-thickness skin defects are characterized based on the local AEs observed on RECELL-treated areas, control areas, RECELL-treated donor sites, and non-RECELL-treated donor sites. The overall safety evaluation of the ITT population did not raise any concerns.

No unanticipated adverse device effects or serious device-related events were reported. The number of subjects with any treatment-emergent adverse event (TEAE) at the RECELL treatment site was similar to the number of subjects with any TEAE at the Control treatment area (36/65, 55.4% and 37/65, 56.9%, respectively). Twenty-one subjects had TEAEs reported in areas that were not involved in the study treatments (32.3%). Most subjects experienced TEAEs that were mild (67.7%) or moderate (26.2%). There was no overt difference between RECELL and Control in the incidence of TEAEs at the treatment area (impaired healing, pain, graft loss, and skin graft failure). The most common TEAE at both the RECELL and Control treatment areas was impaired healing, experienced by 16 (24.6%) subjects. One or more severe TEAEs were experienced by 11 (16.9%) subjects; however, no severe TEAE was related to the RECELL device. Twenty-six subjects had serious adverse events (SAEs), and four died as a result of the SAEs (all were severe and not related to the study device). No SAE was related to study treatment.

#### Retrospective Review of Patients $\geq 18$ Years of Age with $>50\%$ TBSA Acute Full-thickness Thermal Injury

There were no unanticipated adverse device effects or adverse events attributed to RECELL use. Mortality rates were similar between the RECELL Cohort (18.4%) and the NBR Control (20.2%). The incidence of infection and graft failures was greater in the RECELL Cohort compared to the RCT Control, which was anticipated due to greater burn size in the RECELL Cohort. Beyond Week 8, there was no occurrence of spontaneous breakdown of the treated areas in either the RECELL Cohort or RCT Control. Table 6 summarizes the key safety

events in patients  $\geq 18$  years of age with  $>50\%$  TBSA acute thermal burn wounds in the RECELL Cohort and RCT Control.

Table 6 – Key Safety Events in RECELL Cohort and RCT Control in Patients  $\geq 18$  Years of Age with  $>50\%$  TBSA Acute Thermal Injury

<b>Key safety Event</b>	<b>RECELL Cohort (N= 49) Number of (%) Subjects with Event</b>	<b>RCT Control (N=28) Number of (%) Subjects with Event</b>
Graft Infection	7 (14.3%)	1 (3.6%)
Graft Failure	4 (8.2%)	1 (3.6%)
Graft Loss/Impaired Healing	9 (18.4%)	5 (17.9%)

Retrospective Review of Patients  $<18$  Years of Age with Acute Full-thickness Thermal Injury

No unanticipated adverse device effects or adverse events attributed to the use of RECELL were reported. Mortality rates were comparable between the RECELL Cohort (0%) and the NBR Control (0.4%). The incidence of treatment-related adverse events (graft infection, graft failure and graft loss/impaired healing) was greater in the pediatric RECELL Cohort compared with the adult RCT Control. This was anticipated due to greater burn size and increased number of treatment areas in the pediatric RECELL Cohort, providing a greater opportunity for treatment-area complications. The proportion of patients experiencing at least one key safety event was similar between two groups, i.e., 17.9% in the pediatric RECELL Cohort and 20.0% for adult RCT Control. Table 7 summarizes the key safety events in subjects age  $<18$  years in the RECELL Cohort and RCT Control.

Table 7 – Key Safety Events in RECELL Cohort and RCT Control in Subjects  $<18$  Years of Age in the

RECELL Cohort and RCT Control with Acute Full Thickness Thermal Injury

<b>Key safety Event</b>	<b>Pediatric RECELL Cohort (N= 39) Number of (%) Subjects with Event</b>	<b>RCT Control (N=30) Number of (%) Subjects with Event</b>
Graft Infection	5 (12.8%)	2 (6.7%)
Graft Failure	3 (7.6%)	2 (6.7%)
Graft Loss/ Impaired Healing	6 (15.4%)	3 (10%)
Experienced at least 1 key safety event	7 (17.9%)	6 (20.0%)

Retrospective Analysis of Patients with Full-Thickness Thermal Injury over Joints (Including Hands)

No unanticipated adverse device effects or serious adverse events attributed to the use of RECELL were reported. The collection of safety data was limited due to the observational nature of the expanded access protocol and the retrospective analysis based on the observed data. Both the experiment area and control area received RECELL and skin autografting. Systemic adverse events are not expected, considering the topical route of administration of the autologous cell suspension (RECELL).

***Safety – Additional Endpoints:***

Study CTP001-6

Pre-specified safety events including delayed healing, scar necessitating surgical intervention, allergic response to trypsin, wound durability issue, infection, and pain, were evaluated during the study. There was no difference in the incidence of delayed healing and scar revision surgery at RECELL and Control treatment areas. No patient had either an allergic response to trypsin or a wound durability issue. Infection was not observed at the RECELL treatment areas but was observed at two Control treatment sites; however, the numbers were too small for any conclusion to be drawn regarding infection and treatment. No clinically meaningful difference was observed in the degree of pain associated with the two treatments.

Study CTP001-5

There was no overt difference in the incidence of graft loss and graft and donor

site infection between the RECELL and the Control sites at any time point. Recipient site scarring was measured by mean total Vancouver Scar Scale (VSS) scores, and there were no differences between the two recipient sites. The RECELL donor sites had improved appearance at all time points, based on the numerical comparisons of VSS total score outcomes between treatment and Control. Long-term durable wound healing was achieved for both the RECELL treated and control wounds, as no events of late wound breakdown were reported.

***Device Failures:***

Study CTP001-5

A total of 138 devices were used under clinical study CTP001-5, with 125 used successfully. Root cause analysis identified four device malfunctions attributable to (b) (4) causing electrical shorting in either the heating (b) (4) or the (b) (4). Three (3) device failures were determined to be the result of (b) (4) associated with reported malfunctions of “failed during self-test” and “failed during use”. Investigation revealed (b) (4) in the heating (b) (4) which resulted from the use of an incorrect (b) (4) during device manufacturing. One device that was returned to AVITA under CTP001-5 due to expiration was incorrectly reported as a malfunction. For the remaining 4 devices returned due to reported malfunction, the root cause investigation was either inconclusive, unresolved, or no problem was found.

Study CTP001-6

A total of 34 devices were used under Study CTP001-6, 32 used successfully with 2 device malfunctions reported. Root cause analysis performed in association with the 2 reported device failures was either inconclusive/unresolved or no problem was found.

Study CTP007

A total of 67 devices were used under Study CTP007, and no device malfunctions were reported.

Study CTP004 (Expanded Access)

A total of 389 devices were used under Study CTP004, 371 used successfully, 16 device malfunctions reported, and 2 devices were opened in the operating room and not used. Root cause analysis performed in association with the 16 reported device failures was either associated with the heating element, user error, inconclusive/unresolved or no problem was found.

Study CTP001-8 (Continued Access)

A total of 146 devices were used under study CTP001-8, 143 used successfully, with 3 device malfunctions reported. Root cause analysis performed in association with the 3 reported device failures was either an over temperature alarm or user error.

CTP004 and CTP001-8, clinical outcomes were unaffected given the device failures occurred either after the patient had been treated or at a stage when an additional RECELL device could be used to complete the procedure successfully.

## 2. Effectiveness Results

### Study CTP001-6

The co-primary endpoints for this study were non-inferiority of RECELL plus autograft relative to autograft control, at the recipient sites at Week 8 and superiority in sparing of donor site skin for RECELL relative to control at the time of treatment.

Non-inferiority of RECELL relative to Control for recipient site healing was established using the pre-specified non-inferiority margin of 10%. Confirmed treatment area closure by Week 8 was 92.3% for RECELL vs. 84.6% for the Control treatment areas. The treatment difference was - 7.7% (Control minus RECELL, 95% CI upper bound of 9.55%).

Superiority of RECELL was established with respect to relative reduction in donor site harvesting ( $p < 0.001$ ). The mean donor site areas for RECELL and Control were  $270.5 \pm 123.7 \text{ cm}^2$  and  $368.0 \pm 150.1 \text{ cm}^2$ , respectively. Secondary effectiveness outcomes (patient satisfaction, Week 24 observer overall opinion on POSAS, and Week 24 patient overall opinion on POSAS) were comparable between treatments.

### Study CTP001-5

The co-primary endpoints for this study were non-inferiority of RECELL, relative to autograft control, at the recipient sites at Week 4 and superiority of donor site healing for RECELL relative to control at Week 1.

At Week 4, 94.3% of the RECELL recipient sites achieved healing vs. 100% of the Control recipient sites. Although comparable numbers were achieved, the primary endpoint of non-inferiority of RECELL relative to Control for recipient site healing was not established in the per protocol population using the pre-specified non-inferiority margin of -10% (RECELL minus Control; difference - 5.7%, 95% CI: -12.8% to -0.4%).

When evaluating a Modified per protocol population (MPP) (post-hoc analysis), defined to exclude the subjects managed post-operatively with silver sulfadiazine (a cytotoxic agent), the difference in proportions for complete wound healing between the RECELL and Control recipient areas established non-inferiority for RECELL compared with Control treatment (RECELL minus Control difference was -2.4%, 95% CI: -8.4 to 2.3%). The MPP analysis provides evidence that when RECELL-treated sites receive appropriate aftercare, healing is non-inferior to those sites treated with meshed autografts. Donor site healing was superior at

Week 1 for the RECELL donor sites versus the Control donor sites ( $p=0.0042$ ). Subjects reported less pain at the RECELL donor site compared to the Control donor site at every time point within the 8 weeks following treatment. Similarly, subjects expressed greater satisfaction with the visual appearance of the RECELL donor site compared with the Control donor site at all longer-term follow-up visits. The mean donor site area for RECELL was substantially less than that of the Control:  $4.7 \pm 3.19 \text{ cm}^2$  vs  $194.1 \pm 158.5 \text{ cm}^2$ , respectively.

#### Study CTP007

The efficacy evaluation is based on the coprimary endpoints: (1) noninferiority of RECELL-treated areas compared to control-treated areas in promoting complete wound closure by Week 8 in the PP population; and (2) superiority of relative reduction in donor area requirements of RECELL-treated areas compared to control-treated areas in ITT population.

The wound closure endpoint was defined as the difference in proportion of complete closure in RECELL-treated areas and control-treated areas by (or prior to) Week 8, confirmed at two consecutive study visits at least 2 weeks apart (at Week 6 and Week 8; at Week 8 and Week 10; or at Week 8 and Week 12 if the Week 10 visit was missed), assessed by a blinded evaluator, in the PP population. To establish the noninferiority of RECELL to control, the upper bound of the one-sided 97.5% confidence interval (CI) needs to be less than 10%. Among the 52 subjects in the PP population, 34 subjects in the RECELL group and 30 subjects in the control group achieved complete wound closure by 8 weeks. The treatment difference (control minus RECELL) was -7% with a one-sided 97.5% CI upper bound of 6.2%. The noninferiority of RECELL-treated areas compared to control-treated areas in promoting complete wound closure is demonstrated.

The donor area requirements endpoint was defined as the ratio of actual expansion ratios: the ratio (RECELL to control) of the measured treatment area (size) to the measured donor skin area (i.e., RECELL-treated area/corresponding donor area to control-treated area/corresponding donor area, including donor skin needed for secondary treatments) in the ITT population. A geometric mean ratio (GMR of ratios) with a lower bound of the 95% CI exceeding 1 would indicate superiority of RECELL to control. The GMR was 1.36 with a lower bound of the 95% CI of 1.27 ( $p<0.001$ ). The superiority of RECELL to control in reducing the donor area requirements is demonstrated.

#### Retrospective Review of Patients $\geq 18$ Years of Age with $>50\%$ TBSA Acute Full-thickness Thermal Injury

Median number of autograft treatments required for definitive closure in the RECELL Cohort (2.0 treatments, range 1.0-6.0) was lower than in the NBR Control (5.0 treatments, range 1.0-32.0). The difference was significant at the conventional 0.05 statistical significance level.

Mean number of autograft treatments required for definitive closure in the RECELL Cohort was 2.4 treatments (SD 1.3) and in the NBR Control was 5.9 treatments (SD 4.6). The difference was significant at the conventional 0.05 statistical significance level.

Median Length of Hospital Stay was 1.2 days per %TBSA (range 0.6-3.0) in the RECELL Cohort and 1.2 (range 0.5-6.3) within the NBR Control (p= 0.60). By Week 8 after treatment, 90.6% of the wounds treated in the RECELL Cohort achieved  $\geq 95\%$  re-epithelialization.

#### Retrospective Review of Patients <18 Years of Age with Acute Full-thickness Thermal Injury

Median number of autograft treatments required for definitive closure in the pediatric RECELL Cohort (1.0 treatment) was lower than in the NBR Control (2.0 treatments). Mean number of autograft treatments required for definitive closure was 1.6 treatments (SD 1.1) in the RECELL Cohort, and was 3.6 treatments (SD 3.7) in the NBR Control. The difference was significant at the conventional 0.05 statistical significance level.

Median Length of Hospital Stay was 1.7 days per %TBSA (range 0.6-3.3) in the pediatric RECELL Cohort and 1.2 (range 0.5-3.9) in the NBR Control. By Week 8 after treatment, 91.8% of wounds treated in the RECELL Cohort achieved  $\geq 95\%$  re-epithelialization.

#### Retrospective Analysis of Patients with Full-Thickness Thermal Injury over Joints (Including Hands)

The wound closure was defined as 100% re-epithelialization by Week 8 confirmed at 2 consecutive visits. The proportion of wound closure was estimated by the Least-Squares means (LSMEANS) method with a repeated measures generalized estimating equation (GEE) model. By Week 8, wound closure was achieved in 55.84% of RECELL-treated wounds involving joints/hands compared with 60.59% of RECELL-treated wounds not involving joints/hands.

Despite inherent limitations of retrospective analyses from an expanded use protocol and missing data of wound size of approximately half of RECELL-treated areas including joints/hands (experiment) and the RECELL-treated areas not including joints/hands (control), there were no appreciable differences with respect to effectiveness of the RECELL Device for the treatment of full-thickness burn wounds in areas including joints/hands and the areas not including joints/hands.

### 3. Subgroup Analyses

#### Study CTP001-6

The study population was mostly comprised of White adult males. Due to the small sample size and the relative homogeneity of the study population, no conclusions can be drawn regarding outcomes for subgroups based on sex, age, and ethnicity.

#### Study CTP001-5

The limited sample size and the relatively homogeneous study population limit the ability to draw conclusions regarding the safety or efficacy of RECELL in subgroups based on age, sex, or race.

#### Study CTP007

No subgroup analyses were conducted in this study due to the small sample size.

#### Retrospective Review of Patients $\geq 18$ Years of Age with $>50\%$ TBSA Acute Full-thickness Thermal Injury (Study CTP004)

Due to the small sample size and the relative homogeneity of the study population, no conclusions can be drawn regarding outcomes for subgroups based on sex, age and ethnicity.

#### Retrospective Review of Patients $<18$ Years of Age with Acute Full-thickness Thermal Injury (Studies CTP004 and CTP001-8)

Due to the small sample size and selection of a relatively homogeneous pediatric study population, no further conclusions can be drawn regarding outcomes for subgroups based on sex, age, and ethnicity.

#### Retrospective Analysis of Patients with Full-Thickness Thermal Injury over Joints (Including Hands)

Due to the small sample size no further conclusions can be drawn regarding outcomes for subgroups based on sex, age, and ethnicity.

### 4. Pediatric Extrapolation

#### Study CTP001-6

Although this study did enroll pediatric subjects age 5 years and older, the youngest study subject was nine years old, and only three study subjects were younger than 18 years. Thus, there is an insufficient amount of data to assess the safety and efficacy of RECELL for treating full-thickness acute thermal burn wounds in pediatric subjects.

#### Study CTP001-5



Pediatric study subjects younger than 18 years of age were excluded.

#### Study CTP007

The youngest study subject was 15 years old, which is reflected in the Indication for use. Thus, there is insufficient amount of data to assess the safety and efficacy of RECELL for treating full-thickness skin defects in pediatric patients younger than 15 years of age.

#### Retrospective Review of Patients <18 Years of Age with Acute Full-thickness Thermal Injury

In the original premarket application, existing clinical data were not able to be leveraged to support approval of a pediatric patient population younger than 18 years of age. The Applicant submitted a panel-track labeling supplement including safety and efficacy data from retrospective analysis on data from 39 pediatric patients younger than 18 years of age with acute full-thickness thermal burn wounds, who received the RECELL Device in the Expanded Access Protocol CTP004, conducted under IDE 15945.

### **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. As certified in the FORM FDA 3454 submitted by the applicant, none of the 117 clinical 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**

The Applicant submitted supplemental safety and efficacy data from retrospective analyses on data from: 1) 39 pediatric patients younger than 18 years of age with acute full-thickness thermal burn wounds, who received the RECELL Device in the Expanded Access Protocol CTP004, conducted under IDE 15945, and Continued Access, Pediatric Protocol CTP001-8 under IDE 13053; 2) 49 patients 18 years of age and older with acute full-thickness thermal burn wounds involving >50% of total body surface area (TBSA), who received the RECELL Device in Expanded Access Protocol CTP004; and 3) 61 patients with acute full-thickness thermal burn wounds involving joints (including hands), who received the RECELL Device combined with meshed autograft in Expanded Access Protocol CTP004.

## **XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION**

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this panel-track labeling supplement was not referred to an FDA advisory committee for review and recommendation because it was judged that the expertise of the FDA PMA review staff was sufficient to determine there is a reasonable assurance the device is safe and effective based on the information provided in the supplemental PMA application, when used in accordance with the indications for use for: (1) Treatment of pediatric and adult patients with full-thickness thermal burn wounds, in combination with meshed autografting; (2) Treatment of partial-thickness thermal burn wounds in patients age 18 years and older ( $\geq 18$  years); and (3) Treatment of full-thickness skin defects after traumatic avulsion (e.g., degloving) or surgical excision (e.g., necrotizing soft tissue infection) or resection (e.g., skin cancer) in patients 15 years of age and older ( $\geq 15$  years), in combination with meshed autografting.

### **XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES AND EXPANDED ACCESS DATA**

#### **A. Effectiveness Conclusions**

The effectiveness of RECELL as an autograft-sparing technology capable of achieving definitive wound closure is substantiated through results derived from three separate AVITA Medical-sponsored US multicenter, randomized, controlled clinical studies. For the treatment of acute thermal burn wounds, the clinical studies collectively provided experience for 131 patients for a 52-week period following treatment. The use of RECELL either as a primary or adjunct intervention to meshed skin grafts, results in wound closure that is non-inferior to that achieved with conventional autografts, with substantially less donor site harvesting requirements (97% reduction in donor skin area in CTP001-5, approximately 30% in CTP001-6, and 27% in CTP007).

The RECELL Device demonstrated reasonable assurance of effectiveness in reducing the donor area requirements and in promoting wound closure in combination with meshed autografting for various full-thickness skin defects in Study CPT007.

Together with the smaller donor site taken for the RECELL process (compared to autografting), the donor site was determined to heal faster than the donor site for the conventional autograft and was associated with less pain, improved appearance, and patient satisfaction (CTP001-5). During the follow-up period of 52 weeks, there were no events of recurrent wound breakdown following closure, indicating durable wound healing.

Among the two thermal burn studies and the one full-thickness skin defect study presented, there were no differences between RECELL and the control treatment with respect to the type of complications of concern for autografting procedures -- i.e., graft loss or graft failure, impaired healing, infection, or scarring. Within the CTP001-5 study, only 1 of the 101 subjects (1%) treated with Spray-On Skin Cells required subsequent re-grafting for healing. Within the CTP001-6 protocol, 2

(7%) subjects treated with RECELL required a secondary grafting procedure, whereas 3(10%) of Control subjects required re-grafting.

In Study CTP007, three subjects received retreatment with autografts. None of the three subjects achieved complete wound closure for RECELL-treated or control-treated areas by Week 8 and all the three had major protocol deviations; therefore, these three subjects were excluded from the PP population. The reasons for retreatment were graft loss or graft failure.

Efficacy of RECELL Device in treatment of (1) full-thickness acute thermal burn wounds involving >50% TBSA in patients age  $\geq 18$  years; and (2) full-thickness acute thermal burn wounds in pediatric patients <18 years of age, is based on the reduction in the median number of autograft treatments required for definitive wound closure when comparing data obtained within Expanded and Continued Access Protocols (RECELL Cohort) and matched external control cohorts of patients in the American Burn Association's National Burn Repository (NBR). The median number of autograft treatments required for definitive closure in the adult extensive burns analysis was 2.0 treatments (range 1.0-6.0), for the RECELL Cohort versus 5.0 treatments (range 1.0-32.0), for the NBR Control. In the pediatric RECELL Cohort, median number of autograft treatments required for definitive closure was 1.0 treatment (range 1 to 5), versus 2.0 treatments (range 1 to 20) in the NBR Cohort.

Effectiveness analysis of RECELL Device in treatment of full-thickness thermal burn wounds involving joints (including hands) is based on the Week 8 wound closure data comparing RECELL-treated wounds involving joints (including hands) compared with RECELL-treated wounds not involving joints (including hands). Despite inherent limitations of a retrospective analysis of data from an expanded access protocol to include missing data, there were no appreciable differences with respect to wound closure with the use of RECELL combined with meshed autograft for the treatment of wounds in areas involving joints (including hands) and the areas not involving joints (including hands).

## **B. Safety Conclusions**

The risks of the device were based on non-clinical bench testing and animal studies as well as data collected in clinical studies conducted to support the original PMA approval as described above. Within randomized studies, adverse events documented were both anticipated and consistent with a patient population undergoing autografting for treatment of thermal burn injuries and full-thickness skin defects after traumatic avulsion, surgical excision or resection.

In the retrospective analyses of data from open-label expanded access and continued access studies, no unanticipated adverse device effects or adverse events attributed to the use of RECELL were reported. Mortality rates were comparable between the RECELL Cohort and the NBR Control in patients age  $\geq 18$  years full-thickness acute thermal burn wounds involving >50% TBSA (18.4% vs 20.2%,

respectively) and in pediatric patients <18 years of age with full-thickness acute thermal burn wounds (0% vs. 0.4%, respectively). The incidence of treatment-related adverse events (graft infection, graft failure and graft loss/impaired healing) was greater in both RECELL Cohorts compared with the adult RCT Control. This was anticipated due to greater burn size and increased number of treatment areas in both RECELL Cohorts. There were no appreciable differences with respect to safety with the use of RECELL combined with meshed autograft for the treatment of full-thickness thermal burns in the areas involving joints (including hands) and the areas not involving joints (including hands).

### **C. Benefit-Risk Determination**

In addition to three adequate and well-controlled clinical studies, two retrospective analyses were conducted to generate safety and effectiveness data to support panel-track labeling supplement PMA approval in the intended pediatric and adult patient populations, as described above. The data provide a reasonable assurance of safety and effectiveness for RECELL as an autograft-sparing technology indicated for use at the patient's point-of-care for preparation of an autologous skin cell suspension to be applied to a prepared wound bed. When used by a licensed healthcare professional at point-of care, the suspension can be used to achieve epithelial regeneration for definitive closure of acute thermal burn injuries and full-thickness skin defects after traumatic avulsion, surgical excision or resection. Furthermore, these data support a low rate of device-related adverse events.

Potential challenges with RECELL system use and patient post-discharge wound care were identified during the three clinical trials. To minimize the possibility that adverse effects that could result from insufficient familiarity with the recommended procedures for device use and post-discharge wound care, the Applicant developed a health care practitioner training program, as well as post-discharge patient education material.

Clinical data demonstrate that the risks associated with RECELL use are low and consistent with complications of standard autograft treatment such as potential for non-healing, graft loss, infection and scarring. The benefits derived from the use of the device, i.e., definitive wound closure of larger burn surfaces with a smaller donor site defect outweigh the potential for harm. The two retrospective analyses provided in the panel-track supplement, did not identify additional safety risks with the use of RECELL in treatment of full-thickness acute thermal burns in the special populations of patients younger than age 18 years and patients age  $\geq 18$  years with burn wounds involving >50% TBSA.

In Study CTP007, the RECELL Device demonstrated reasonable assurance of effectiveness in reducing the donor area requirements and promoting wound closure in combination with meshed autografting for full-thickness skin defects after traumatic avulsion (e.g., degloving) or surgical excision (e.g., necrotizing soft tissue infection) or resection (e.g., skin cancer), in patients 15 years of age and older. The overall safety profile did not raise any concerns and does not warrant

any post-approval or post-market surveillance studies.

Thus, when RECELL is used in accordance with instructions for use and patient wound care is performed according to the recommended methods, the benefits associated with use of the RECELL Device outweigh the risks.

**D. Overall Conclusions**

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

**XIV. CBER DECISION**

CBER issued an approval order on [December 22, 2023].

***Manufacturing Facility Pre-Approval Inspection***

During review of the PMA application, the determination was made to recommend waiver of the pre-approval inspection of the applicant's manufacturing facilities. This decision was based on information provided in the PMA application in conjunction with prior inspection reports and related correspondence supporting the overall compliance of the applicant's registered manufacturing facilities with the device Quality System (QS) regulation (21 CFR 820).

**XV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

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

**XVI. REFERENCES**

None