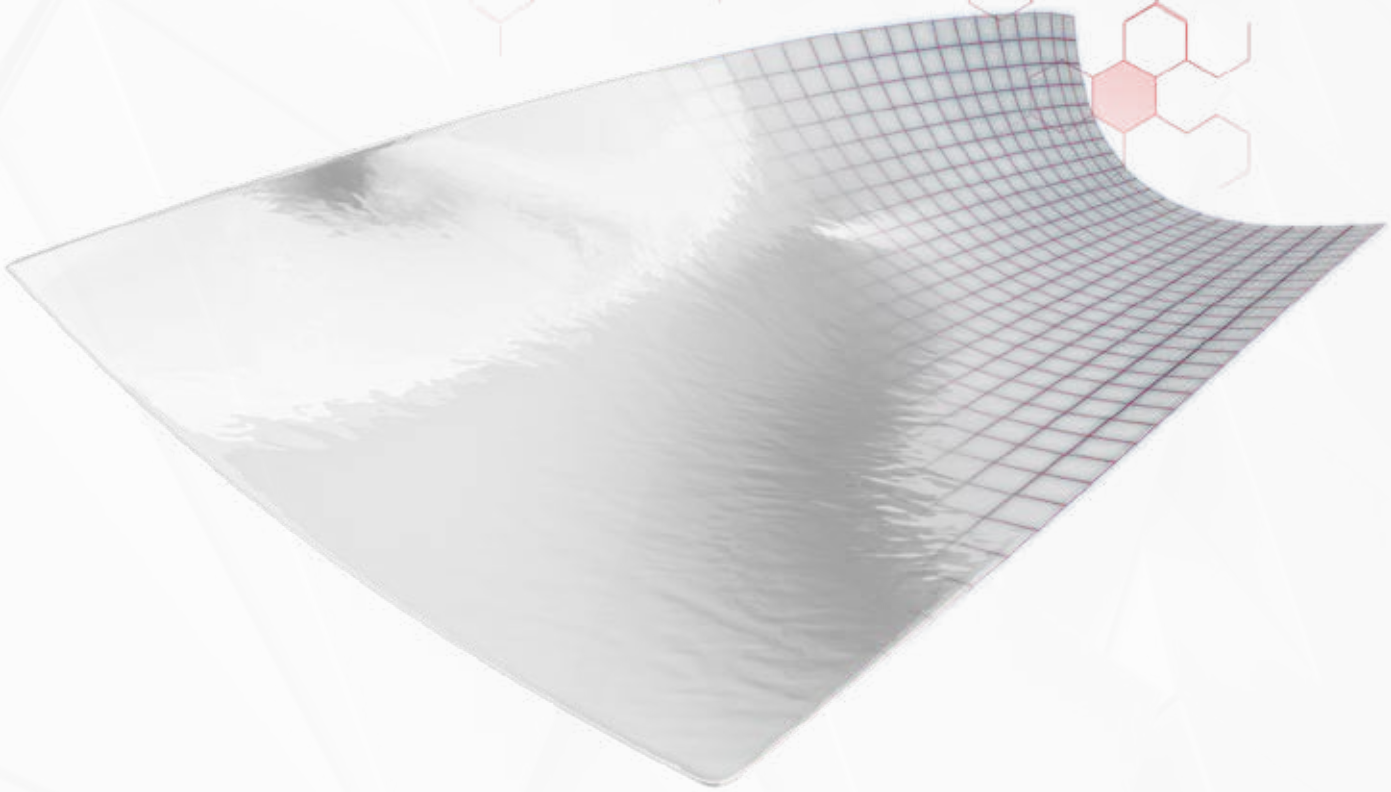
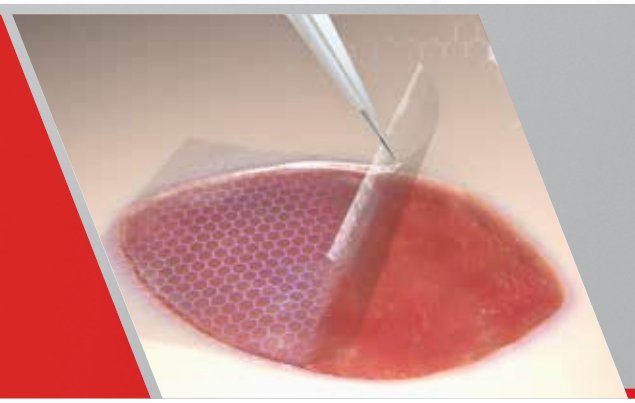


BIOSKIN®

Amniotic Wound Matrix



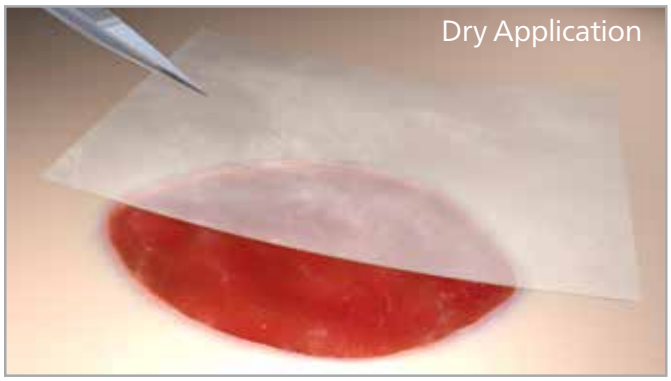
PRESERVE AND PROTECT

TECHNOLOGY OVERVIEW
FOR HOSPITAL VALUE
ANALYSIS COMMITTEE

WRIGHT™
FOCUSED EXCELLENCE

BIOSKIN® is Wright's amniotic wound matrix that provides comprehensive preservation of native amniotic tissue proteins to deliver a biologic scaffold to support clinical efforts for challenging wound treatment and accomodate covering and protecting both acute and chronic wounds.

Protects Wounds

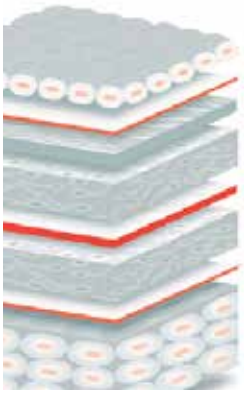


BIOSKIN® offers optimized handling to ensure tissue application and coverage is simple and reproducible regardless of the wound geometry or location.

- Tissue Thickness: ~200um
- Easy to see and manipulate
- Omni-directional application
- Wet or dry application
- Room temperature storage

BIOSKIN® matrix sheets utilize placental tissue to deliver a product that provides a sturdy yet supple biologic matrix. BIOSKIN® matrix sheets perform consistently regardless of application environment and allow for easy application and conformity to the wound bed.

Placental Tissue Composition



Preserves Biology

BIOSKIN® utilizes the HydraTek® process designed to select and preserve tissue that retains and delivers the same extraordinary wound benefits observed natively *in-vivo*.

- **Biologic Potential** Retains high levels of growth factors and collagens.†
- **Immunosuppressive** Retains the natural features that allow the body to suppress inmune responses and excessive inflammation.†
- **Fast Acting** Designed to resorb faster and go to work quicker.†
- **Antimicrobial** Shown to be bacterostatic against certain bacteria in vitro.†

Growth Factor Content

	BIOSKIN®	Native Tissue
TIMP-1	X	X
TIMP-2	X	X
VEG F	X	X
TGF-β1	X	X
TGF-β2	X	X
TGF-β3	X	X
IL-4	X	X
PIGF	X	X
KGF	X	X
EGF	X	X
bFGF	X	X
PDGF-AA	X	X
PDGF-BB	X	X

Less Than **1.5%** Collagen Loss*†

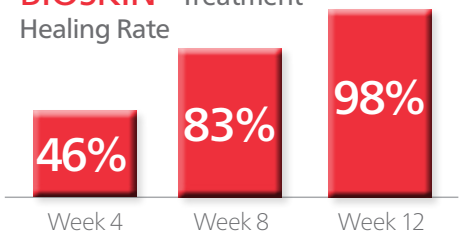
*By Weight

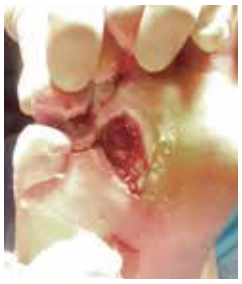
†Data on File at HRT

Clinical Evidence*,‡

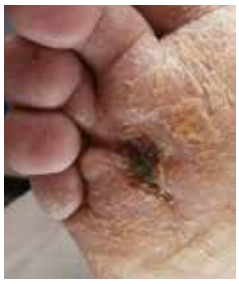
BIOSKIN® covers and protects acute and chronic wounds to support clinical efforts to repair wounds.

- **9.9 weeks** average to full wound closure observed over 20 patients
- **7.4cm²** average size wound treated
- **2.5** average applications to close

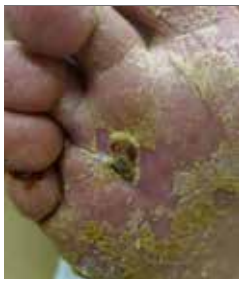




Post-Debridement
3cm x 1.5cm x 0.4cm
One application BIOSKIN®



Week 10



Week 12
100% Closure

*Lulove EJ. Use of a Dehydrated Amniotic Membrane Allograft in the Treatment of Lower Extremity Wounds: A Retrospective Cohort Study. Wounds. 2017 Nov; 29(11): 346-51.

‡Study refers to WoundEx. BIOSKIN® is identical to WoundEx. HRT processes both these tissues.

BIOSKIN® Amniotic Wound Matrix Clinical Study Summary

Evaluation of BIOSKIN® Effectiveness in Treating Chronic Ulceration of the Lower Extremities*,†

20 Patients Enrolled

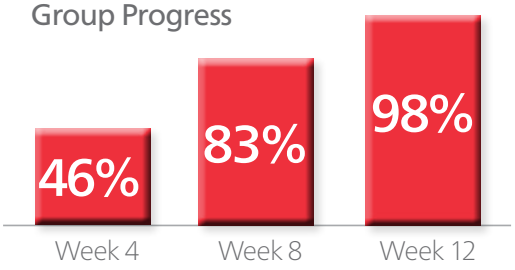
>4 Week Nonhealing Wounds

0 Prior Cellular Tissue Used

Is BIOSKIN® effective for lower extremity wounds?

- Retrospective single center, single investigator study of 20 randomly selected patients.
  - Inclusion criteria: Minimum of 4 weeks non-healing chronic lower extremity wound (DFU, VLU, etc.)
  - Exclusion criteria: Acute infection, prior use of any cellular tissue product (CTP), or ankle-brachial index (ABI) less than 0.6
- Standard of care to address bioburden for first 2 weeks.
- BIOSKIN® applied following two week bioburden treatment in week 1, 3, and 5 until closure and data recorded weekly.

BIOSKIN® Treatment Group Progress



98% Closure Rate

7.4cm² Average Wound Size

2.5 Average Number of Applications

Results

- 98% closure rate at 12 weeks
- 7.4cm² average wound size
- 2.5 average BIOSKIN® applications to closure
- Average wound healing time 69.3 days (9.9 weeks)

Conclusion

BIOSKIN® use in wound treatment was supported for patients with lower extremity wounds involving the venous system with chronicity greater than 4 weeks.

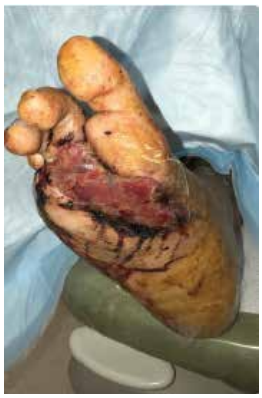
**Lullove EJ. Use of a Dehydrated Amniotic Membrane Allograft in the Treatment of Lower Extremity Wounds: A Retrospective Cohort Study. Wounds. 2017 Nov; 29(11): 346-351.*

†Study refers to WoundEx. BIOSKIN® is identical to WoundEx. HRT processes both these tissues.

BIOSKIN® Clinical Healing Progression Example for a Complicated Chronic Wound†

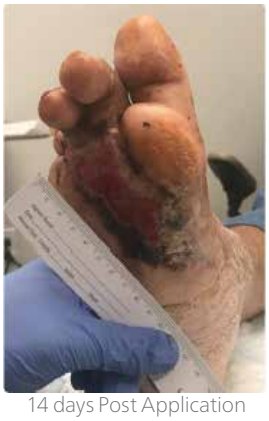
Clinic Visit
Wound Size: 6x17cm

Graft Application
Plantar surface

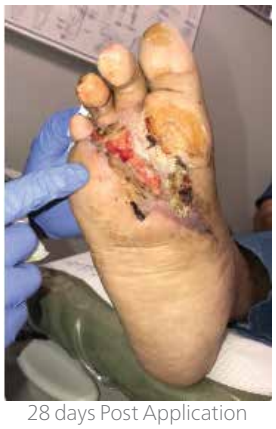


4 days Post Application
Wound Size: 3x9cm

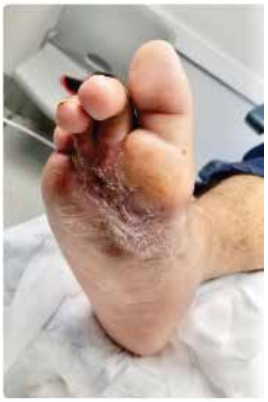
43 year old male diabetic type 2 patient with a 4x8cm infected chronic wound originating from a small unnoticed acute injury struggled through 6 months with the non-healing wound. The infection was addressed in the first two weeks of treatment and 1x BIOSKIN® matrix was applied at this time. Following application, wound progressed to closure in 9 weeks.



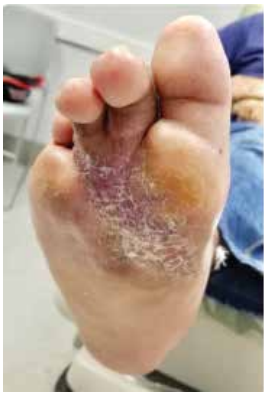
14 days Post Application
Wound Size: 2x7cm



28 days Post Application
Wound Size: 1.5x7cm



49 days Post Application
Wound Size: 0 cm



63 days Post Application
Complete Re-epithelialization

†Data on File at HRT.

HydraTek® Processing*

HydraTek® post-processed tissues were examined for structural and bioactive components and reviewed for biologic impacts to wound environments

Collagen Retention
Less than 1.5% loss

Immuno-suppressive
Based on INF- γ levels

Growth Factor Retention
ELISA verified

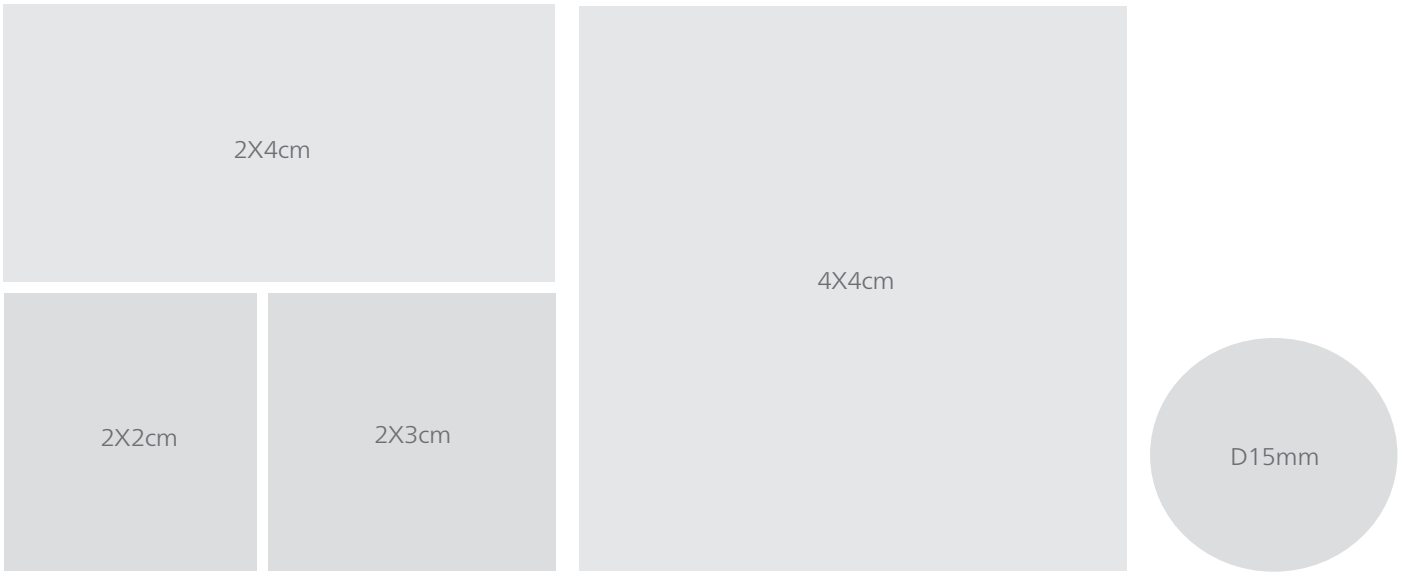
Anti-Microbial
Bacteriostatic against some bacteria

The outcomes for these tests demonstrated characteristics of post-processed HydraTek® tissues that suggest relevant and beneficial use in wound treatment.

**Irvin J, Danchik C, Rall J, Babcock A, Pine M, Barnaby D, Pathakamuri J, Kuebler D. 2018. Bioactivity and composition of a preserved connective tissue matrix derived from human placental tissue. J Biomed Mater Res Part B Appl Biomater. 2018 Nov; 106(8): 2731-2740.*

BIOSKIN® Ordering Information

Product No.	Description
WA204X04	BIOSKIN® 4X4cm
WA202X04	BIOSKIN® 2X4cm
WA202X03	BIOSKIN® 2X3cm
WA202X02	BIOSKIN® 2X2cm
WA20D015	BIOSKIN® DISC 15mm



WRIGHT
FOCUSED EXCELLENCE

1023 Cherry Road
Memphis, TN 38117
USA

901 867 9971
800 238 7117
wright.com

30-May-2019

To whom it may concern,

Per Human Regenerative Technologies LLC's FDA Human Cell and Tissue Establishment Registration (FDA Establishment Identifier (FEI): 3010712680), the BIOSKIN® product family consists of HCT/P's (Human Cells, Tissues, and Cellular and Tissue-Based Products) comprised entirely of placental tissues (listed as amniotic membrane). As 100% human tissue products that meet the criteria described in 21 CFR Part 1271.10 to qualify for regulation under Section 361 of the PHS Act, these HCT/P's are not regulated as medical devices by the FDA and thus do not require a 510k submission. These HCT/P's are regulated by the FDA Federal Code of Regulations 21 CFR Part 1271 and American Association of Tissue Banks (AATB) Standards.

Product codes for these are as follows:

WA204X04	BIOSKIN® 4x4cm
WA202X04	BIOSKIN® 2x4cm
WA202X03	BIOSKIN® 2x3cm
WA202X02	BIOSKIN® 2x2cm
WA20D015	BIOSKIN® Disc 15mm

Sincerely,

Matt Parrish
Sr. Manager Quality Systems

FDA Home Page | Contact eHCTERS Technical Support

HUMAN CELL AND TISSUE ESTABLISHMENT REGISTRATION - Public Query
Establishment Details

Establishment Name and Location

Current Status:	Registered
Last Annual Registration Year:	2019
FDA Establishment Identifier (FEI):	0001043534
Establishment Name:	Wright Medical Technology, Inc.
Address:	1023 Cherry Road
City:	Memphis
State:	Tennessee
Zip:	38117
Country:	United States
Phone:	901-451-6356 ext. 6356

Establishment Functions

Types of HCT/Ps	Recover	Screen	Donor Testing	Package	Process	Store	Label	Distribute
Amniotic Membrane						☑		
Blood Vessel								
Bone						☑		
Cardiac Tissue - non-valved								
Cartilage								
Cornea								
Dura Mater								
Embryo								
Fascia								
Heart Valve								
HPC Apheresis								
HPC Cord Blood								
Ligament								
Nerve Tissue								
Oocyte								
Ovarian Tissue								
Pancreatic Islet Cells - autologous								
Parathyroid								
Pericardium								
Peripheral Blood Mononuclear Cells								
Peritoneal Membrane								
Sclera								

Semen								
Skin						☑		
Tendon								
Testicular Tissue								
Tooth Pulp								
Umbilical Cord Tissue						☑		

Establishment HCT/P Listing

Types of HCT/Ps	HCT/Ps Described in 21 CFR 1271.10	Proprietary Names
Amniotic Membrane	X	ActiShield; BIOSKIN?
Blood Vessel		
Bone	X	ALLOMATRIX; ALLOPURE; FUSIONFLEX;IGNITE ; MATRIX OI; OSTEOSET 2 DBM; PROSTIM; TENFUSE; TENSIX; Tricortical Blocks
Cardiac Tissue - non-valved		
Cartilage		
Cornea		
Dura Mater		
Embryo		
Fascia		
Heart Valve		
HPC Apheresis		
HPC Cord Blood		
Ligament		
Nerve Tissue		
Oocyte		
Ovarian Tissue		
Pancreatic Islet Cells - autologous		
Parathyroid		
Pericardium		
Peripheral Blood Mononuclear Cells		
Peritoneal Membrane		
Sclera		
Semen		
Skin	X	GRAFTJACKET; TENSIX ADM
Tendon		
Testicular Tissue		
Tooth Pulp		
Umbilical Cord Tissue	X	ViaFlow

HCT/P Listing - Donor Information

Types of HCT/Ps	SIP	Directed	Anonymous	Autologous	Family Related
Embryo					
HPC Apheresis					
HPC Cord Blood					
Oocyte					
Peripheral Blood Mononuclear Cells					
Semen					

Print Date: 05/29/2019

Print This Page | Back To Query Criteria Screen | Back To Query Results Screen

Exit

eHCTERS v02.10.00
11/09/2018

American Association of Tissue Banks

Herewith certifies
that the Institution named here

Wright Medical Technology, Inc.
Arlington, TN

has met the Association's accreditation requirements and is hereby accredited for Processing, Release, Storage and Distribution of Musculoskeletal Tissue for Transplantation; Storage and Distribution of Skin for Transplantation; and Storage and Distribution of Birth Tissue for Transplantation

July 19, 2018 – April 15, 2021

In witness whereof the undersigned officers, being duly authorized, have caused this Certificate to be issued and the Corporate Seal of this Association to be affixed hereon this the 19th day of July 2018

Louis E. Barnes III

Chairman

President & Chief Executive Officer

Accreditation # 00123/6

American Association of Tissue Banks®

August 23, 2018

Ms. Christy Norman, MS, CIA, CTBS, CQA
Tissue Bank Director
Wright Medical Technology, Inc.
11576 Memphis Arlington Road
Arlington, TN 38002

Dear Ms. Norman:

On behalf of the Board of Governors, I am pleased to inform you that the American Association of Tissue Banks (AATB) has approved Wright Medical Technology, Inc. for accreditation after you had successfully addressed the nonconformities resulting from the inspection. The accreditation covers Processing, Release, Storage and Distribution of Musculoskeletal Tissue for Transplantation; Storage and Distribution of Skin for Transplantation; and Storage and Distribution of Birth Tissue for Transplantation. Obtaining accreditation by the Association is a most important accomplishment, and we congratulate you and your staff.

The mission of the AATB is to improve and save lives by promoting the safety, quality, and availability of donated human tissue. Our Accreditation Program helps to realize this goal by checking that tissue-banking activities are being performed in an ethical and professional manner consistent with the AATB's *Standards*.

In addition to the special recognition attendant to AATB Accreditation, additional benefits include the following:

- Staff members may attend AATB meetings and workshops at reduced rates;
- Your tissue bank will receive a complimentary copy of future *AATB Standards for Tissue Banking*, when available;
- You may also purchase publications at the membership rate and;
- You may use the AATB Accredited Institution Logo (contact Jason LoVerdi at loverdij@aatb.org for logo and information).

Visit our web site at www.aatb.org to see how you can become involved in the various activities of the AATB.

Your accreditation will expire on April 15, 2021. It will be your responsibility to note this date and re-apply in a manner consistent with the current version of AATB's *Accreditation Policies*. You should request the accreditation application approximately 12 months prior to the expiration of your accreditation and you must submit the completed application no later than nine months prior to the accreditation expiration date.

Please accept our sincerest congratulations on your accreditation. We look forward to your participation in and support of the Association's activities. If there is ever any way in which we can assist you, I hope that you will not hesitate to contact us.

Sincerely,

Frank S. Wilton
President & Chief Executive Officer

Accreditation #00123/6; Accreditation Date: July 19, 2018
Attached: Certificate
Satellite Letter

8200 Greensboro Drive, Suite 320, McLean, VA, 22102
Telephone: (703) 827-9582 Fax: (703) 356-2198 aatb@aatb.org

American Association of Tissue Banks®

August 23, 2018

Ms. Christy Norman, MS, CIA, CTBS, CQA
Tissue Bank Director
Wright Medical Technology, Inc.
11576 Memphis Arlington Road
Arlington, TN 38002

Dear Ms. Norman:

This letter accompanies the accreditation certificate for Wright Medical Technology, Inc. to include the accreditation of the following satellite facilities:

Wright Medical Technology, Inc.
District Service Center – Anaheim
12611 Hiddencreek Way, Unit L
Cerritos, CA 90703

Wright Medical Technology, Inc.
District Service Center – Atlanta
2358 Perimeter Park Drive, Suite 380
Atlanta, GA 30341

Wright Medical Technology, Inc.
District Service Center – Austin
425 Round Rock West Drive, Suite 100
Round Rock, TX 78681

Wright Medical Technology, Inc.
District Service Center – Boston
130 Kerry Place
Norwood, MA 02062

Wright Medical Technology, Inc.
District Service Center – Charlotte
4215 Stuart Andrew Blvd., Suite H
Charlotte, NC 28217

Wright Medical Technology, Inc.
District Service Center – Chicago
2060 Algonquin Road, Suite 700
Schaumburg, IL 60173

Wright Medical Technology, Inc.
District Service Center – Columbus
705 F Lakeview Plaza Blvd
Worthington, OH 43085

Wright Medical Technology, Inc.
District Service Center – Concord
1170 Burnett Ave., Suite D & E
Concord, CA

Wright Medical Technology, Inc.
District Service Center – Dallas
1325 Whitlock Lane, Suite 106
Carrolton, TX 75006

Wright Medical Technology, Inc.
District Service Center – Davie
4960 Southwest 52nd St., Suite 425 & 426
Davie, FL 33314

Wright Medical Technology, Inc.
District Service Center - Denver
7304 South Alton Way, Suite 3L
Centennial, CO 80112

Wright Medical Technology, Inc.
District Service Center – Detroit
24387 Halsted Rd., Unit 1A
Farmington Hills, MI 48335

Wright Medical Technology, Inc.
District Service Center - Escondido
358 State Place
Escondido, CA 92029

Wright Medical Technology, Inc.
District Service Center – Houston
9079 Knight Road
Houston, TX 77054

Wright Medical Technology, Inc.
District Service Center – Kansas City
10577 Lackman Road
Lenexa, KS 66129

Wright Medical Technology, Inc.
District Service Center – New York
525 Executive Blvd.
Elmsford, NY 10523

Wright Medical Technology, Inc.
District Service Center - Orlando
6220 Hazeltine National Dr., Suite 111
Orlando, FL 32822

Wright Medical Technology, Inc.
District Service Center - Philadelphia
3494 Progress Drive, Unit H
Bensalem, PA 19020

8200 Greensboro Drive, Suite 320, McLean, VA, 22102
Telephone: (703) 827-9582 Fax: (703) 356-2198 aatb@aatb.org

Wright Medical Satellite Letter

Wright Medical Technology, Inc.
District Service Center – Phoenix
2327 South Hardy Drive
Tempe, AZ 85282

Wright Medical Technology, Inc.
District Service Center – Seattle
19625 62nd Ave S, Suite C109
Kent, WA 98032

Wright Medical Technology, Inc.
District Service Center – St. Paul
1408 Northland Drive, Suite 307
Medota Heights, MN 55120

Wright Medical Technology, Inc.
District Service Center – Salt Lake City
3939 Wasatch Blvd, Suite 19
Salt Lake City, UT 84124

Wright Medical Technology, Inc.
District Service Center – St. Louis
1854 Larkin Williams Road
Fenton, MO 63026

Refer to: Accreditation # 00123/6; Accreditation Date: July 19, 2018

Sincerely,

Frank S. Wilton
President & Chief Executive Officer

BIOSKIN®

Article	Citation	Level of Evidence	Publication Year
Zelen - IWJ - 2013	Zelen CM, Serena TE, Denoziere G, Fetterolf DE. A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. Int Wound J. 2013 Oct;10(5):502-7.	Level I	2013
Serena - Wound Rep Regen - 2014	Serena TE, Carter MJ, Le LT, Sabo MJ, DiMarco DT; EpiFix VLU Study Group. A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated human amnion/chorion membrane allografts and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. Wound Repair Regen. 2014 Nov-Dec;22(6):688-93.	Level I	2014
Zelen - IWJ - 2014	Zelen CM, Serena TE, Snyder RJ. A prospective, randomised comparative study of weekly versus biweekly application of dehydrated human amnion/chorion membrane allograft in the management of diabetic foot ulcers. Int Wound J. 2014 Apr;11(2):122-8.	Level I	2014
Zelen - Wound Med - 2014	Zelen CM, Serena TE, Fetterolf DE. Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: A long-term follow-up study. Wound Medicine. 2014; 4:1-4.	Level III(?)	2014
Miranda - Eplasty - 2016	Miranda EP, Friedman A. Dehydrated Human Amnion/Chorion Grafts May Accelerate the Healing of Ulcers on Free Flaps in Patients With Venous Insufficiency and/or Lymphedema. Eplasty. 2016 Sep 7;16:e26.	Level III	2016
Snyder - Wounds - 2016	Snyder RJ, Shimozaki K, Tallis A, Kerzner M, Reyzelman A, Lintzeris D, Bell D, Rutan RL, Rosenblum B. A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of Dehydrated Amniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer. Wounds. 2016 Mar;28(3):70-7.	Level I	2016
Bianchi - IWJ -2018	Bianchi C, Cazzell S, Vayser D, Reyzelman AM, Dosluoglu H, Tovmassian G; EpiFix VLU Study Group. A multicentre randomised controlled trial evaluating the efficacy of dehydrated human amnion/chorion membrane (EpiFix(®)) allograft for the treatment of venous leg ulcers. Int Wound J. 2018 Feb;15(1):114-122.	Level I	2018
DiDomenico - IWJ - 2018	DiDomenico LA, Orgill DP, Galiano RD, Serena TE, Carter MJ, Kaufman JP, Young NJ, Jacobs AM, Zelen CM. Use of an aseptically processed, dehydrated human amnion and chorion membrane improves likelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients. Int Wound J. 2018 Dec;15(6):950-957.	Level I	2018
Garoufalis - JAPMA - 2018	Garoufalis M, Nagesh D, Sanchez PJ, Lenz R, Park SJ, Ruff JG, Tien A, Goldsmith J, Seat A. Use of Dehydrated Human Amnion/Chorion Membrane Allografts in More Than 100 Patients with Six Major Types of Refractory Nonhealing Wounds. J Am Podiatr Med Assoc. 2018 Mar;108(2):84-89.	Level III	2018
Tettelbach - IWJ - 2019	Tettelbach W, Cazzell S, Reyzelman AM, Sigal F, Caporusso JM, Agnew PS. A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics. Int Wound J. 2019 Feb;16(1):19-29.	Level I	2019

BIOSKIN BIBLIOGRAPHY:

Selected Dehydrated Human Amnion/ Chorion (DHACM)
Clinical Publications (oldest to newest)

Int Wound J. 2013 Oct;10(5):502-7. doi: 10.1111/iwj.12097. Epub 2013 Jun 7.
A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers.
Zelen CM1, Serena TE, Denoziere G, Fetterolf DE.

Abstract
Our purpose was to compare healing characteristics of diabetic foot ulcers treated with dehydrated human amniotic membrane allografts (EpiFix®, MiMedx, Kennesaw, GA) versus standard of care. An IRB-approved, prospective, randomised, single-centre clinical trial was performed. Included were patients with a diabetic foot ulcer of at least 4-week duration without infection having adequate arterial perfusion. Patients were randomised to receive standard care alone or standard care with the addition of EpiFix. Wound size reduction and rates of complete healing after 4 and 6 weeks were evaluated. In the standard care group (n = 12) and the EpiFix group (n = 13) wounds reduced in size by a mean of 32.0% ± 47.3% versus 97.1% ± 7.0% (P < 0.001) after 4 weeks, whereas at 6 weeks wounds were reduced by -1.8% ± 70.3% versus 98.4% ± 5.8% (P < 0.001), standard care versus EpiFix, respectively. After 4 and 6 weeks of treatment the overall healing rate with application of EpiFix was shown to be 77% and 92%, respectively, whereas standard care healed 0% and 8% of the wounds (P < 0.001), respectively. Patients treated with EpiFix achieved superior healing rates over standard treatment alone. These results show that using EpiFix in addition to standard care is efficacious for wound healing.

Wound Repair Regen. 2014 Nov-Dec;22(6):688-93. doi: 10.1111/wrr.12227. Epub 2015 Jan 8.
A multicenter, randomized, controlled clinical trial evaluating the use of dehydrated humanamnion/chorion membrane allografts and multilayer compression therapy vs. multilayercompression therapy alone in the treatment of venous leg ulcers.
Serena TE1, Carter MJ, Le LT, Sabo MJ, DiMarco DT; EpiFix VLU Study Group.

Abstract
Venous leg ulcers produce significant clinical and economic burdens on society and often require advanced wound therapy. The purpose of this multicenter, randomized, controlled study is to evaluate the safety and efficacy of one or two applications of dehydrated humanamnion/chorion membrane allograft and multilayer compression therapy vs. multilayer compression therapy alone in the treatment of venous leg ulcers. The primary study outcome was the proportion of patients achieving 40% wound closure at 4 weeks. Of the 84 participants enrolled, 53 were randomized to receive allograft and 31 were randomized to the control group of multilayer compression therapy alone. At 4 weeks, 62% in the allograft group and 32% in the control group showed a greater than 40% wound closure (p=0.005), thus showing a significant difference between the allograft-treated groups and the multilayer compression therapy alone group at the 4-week surrogate endpoint. After 4 weeks, wounds treated with allograft had reduced in size a mean of 48.1% compared with 19.0% for controls. Venous leg ulcers treated with allograft had a significant improvement in healing at 4 weeks compared with multilayer compression therapy alone.

Int Wound J. 2014 Apr;11(2):122-8. doi: 10.1111/iwj.12242. Epub 2014 Feb 21.
A prospective, randomised comparative study of weekly versus biweekly application of dehydrated human amnion/chorion membrane allograft in the management of diabetic foot ulcers.
Zelen CM1, Serena TE, Snyder RJ.

Abstract
The aim of this study is to determine if weekly application of dehydrated human amnion/chorion membrane allograft reduce time to heal more effectively than biweekly application for treatment of diabetic foot ulcers. This was an institutional review board-approved, registered, prospective, randomised, comparative, non-blinded, single-centre clinical trial. Patients with non-infected ulcers of ≥4 weeks duration were included for the study. They were randomised to receive weekly or biweekly application of allograft in addition to a non-adherent, moist dressing with compressive wrapping. All wounds were offloaded. The primary study outcome was mean time to healing. Overall, during the 12-week study period, 92·5% (37/40) ulcers completely healed. Mean time to complete healing was 4·1 ± 2·9 versus 2·4 ± 1·8 weeks (P = 0·039) in the biweekly versus weekly groups, respectively. Complete healing occurred in 50% versus 90% by 4 weeks in the biweekly and weekly groups, respectively (P = 0·014). Number of grafts applied to healed wounds was similar at 2·4 ± 1·5 and 2·3 ± 1·8 for biweekly versusweekly groups, respectively (P = 0·841). These results validate previous studies showing that the allograft is an effective treatment for diabetic ulcers and show that wounds treated with weekly application heal more rapidly than with biweekly application. More rapid healing may decrease clinical operational costs and prevent long-term medical complications.

Wound Medicine. 2014; 4:1-4.
Dehydrated human amnion/chorion membrane allografts in patients with chronic diabetic foot ulcers: A long-term follow-up study.
Zelen CM, Serena TE, Fetterolf DE.

Abstract
Diabetic foot ulcers (DFU) are notoriously slow to heal and even in cases where primary healing is achieved ulcers frequently recur. An optimal treatment for DFU would be one that supports both rapid and long-term healing. Our purpose is to evaluate recurrence rates of DFU healed with use of dehydrated human amnion/chorion membrane (dHACM). Twenty-two patients with chronic DFU that healed with the use of dHACM were eligible for inclusion. All eligible patients had completed a single-center randomized clinical trial comparing rates of primary healing over a 12 week period with dHACM versus a standard regimen of care [20] (Zelen et al., 2013). Follow-up examinations were scheduled for 9–12 months after primary healing with dHACM. Subsequent evaluation of clinical records was made with IRB approval and patient consent. Eighteen of 22 eligible patients (81.8%) returned for follow-up examination. Mean wound size prior to treatment with dHACM was 3.1 ± 3.8 cm2, median 1.7 cm2 (0.7, 13.5). Mean time to wound closure after dHACM initiation was 3.1 ± 2.8 weeks (median 2.0 weeks, range 1.0–9.0 weeks). At the 9–12 month follow-up visit 17 of 18 (94.4%) wounds treated with dHACM remained fully healed. These findings support the effectiveness of dHACM for treatment of DFU.

Eplasty. 2016 Sep 7;16:e26. eCollection 2016.
Dehydrated Human Amnion/Chorion Grafts May Accelerate the Healing of Ulcers on Free Flaps in Patients With Venous Insufficiency and/or Lymphedema.
Miranda EP1, Friedman A2.

Abstract

OBJECTIVE:
Ulceration of free flaps in patients with venous insufficiency and/or lymphedema is an uncommon but challenging problem. We hypothesized that dehydrated human amnion/chorion membrane (Epifix) grafts would accelerate healing of these challenging ulcers.

METHODS:
Retrospective analysis of prospectively acquired data identified 8 lower extremity free flaps with ulcerations in the context of venous insufficiency and/or lymphedema. The first 4 were flaps that had been treated with conservative wound care to healing. The second group was treated conservatively initially but then converted to treatment with dehydrated human amnion/chorion membrane grafts. The primary endpoint was time to healing.

RESULTS:
Comparison of Kaplan-Meier survival curves revealed a significant difference between the conservatively and dehydrated human amnion/chorion membrane-treated flap ulcers, favoring graft treatment (P = .0361). In those ulcers that healed, the average time to healingwas 87 days for the conservative treatment group and 33 days for the dehydrated human amnion/chorion membrane treatment group (with an average of 1.7 grafts per ulcer).

CONCLUSIONS:
Dehydrated human amnion/chorion membrane may accelerate healing of ulcers on lower extremity free flaps in patient with lymphedema and/or venous disease in the treated leg.

Wounds. 2016 Mar;28(3):70-7.
A Prospective, Randomized, Multicenter, Controlled Evaluation of the Use of DehydratedAmniotic Membrane Allograft Compared to Standard of Care for the Closure of Chronic Diabetic Foot Ulcer.
Snyder RJ1, Shimozaki K2, Tallis A3, Kerzner M4, Reyzelman A5, Lintzeris D6, Bell D7, Rutan RL8, Rosenblum B9.

Abstract
Delayed closure of foot ulcers is a primary factor leading to lower extremity amputation in patients with diabetes, creating great demand for products or therapies to accelerate the rate of wound closure in this population. This study (ClinicalTrials.gov Identifier: NCT02209051) was designed to evaluate dehydrated amniotic membrane allograft (DAMA) (AMNIOEXCEL, Derma Sciences Inc, Princeton, NJ) plus standard of care (SOC) compared to SOC alone for the closure of chronic diabetic foot ulcers (DFUs).

MATERIALS AND METHODS:
This prospective, open-label, randomized, parallel group trial was implemented at 8 clinical sites in the United States. Eligibility criteria included adults with type 1 or type 2 diabetes mellitus who have 1 or more ulcers with a Wagner

classification of grade 1 or superficial 2 measuring between 1 cm2 and 25 cm2 in area, presenting for more than 1 month with no signs of infection/osteomyelitis; ABI > 0.7; HbA1c Less than 12%; and serum creatinine less than 3.0 mg/dL. Eligible subjects were randomized (1:1) to receive either SOC alone (n = 14) or DAMA+SOC (n = 15) until wound closure or 6 weeks, whichever occurred first. The endpoint was the proportion of subjects with complete wound closure (defined as complete reepithelialization without drainage or need for dressings).

RESULTS:
Thirty-five percent of subjects in the DAMA+SOC cohort achieved complete wound closure at or before week 6, compared with 0% of the SOC alone cohort (intent-to-treat population, P = 0.017). There was a more robust response noted in the per protocol population, with 45.5% of subjects in the DAMA+SOC cohort achieving complete wound closure, while 0% of SOC-alone subjects achieved complete closure (P = 0.0083). No treatment-related adverse events were reported.

CONCLUSION:
The results suggest DAMA is safe and effective in the management of DFUs, but additional research is needed.
Int Wound J. 2018 Feb;15(1):114-122. doi: 10.1111/iwj.12843. Epub 2017 Oct 11.
A multicentre randomised controlled trial evaluating the efficacy of dehydrated humanamnion/chorion membrane (EpiFix®) allograft for the treatment of venous leg ulcers.
Bianchi C1, Cazzell S2, Vayser D3, Reyzelman AM4, Dosluoglu H5, Tovmassian G6; EpiFix VLU Study Group.

Abstract
A randomised, controlled, multicentre clinical trial was conducted to evaluate the efficacy of dehydrated human amnion/chorion membrane (EpiFix) allograft as an adjunct to multilayer compression therapy for the treatment of non-healing full-thickness venous leg ulcers. We randomly assigned 109 subjects to receive EpiFix and multilayer compression (n = 52) or dressings and multilayer compression therapy alone (n = 57). Patients were recruited from 15 centres around the USA and were followed up for 16 weeks. The primary end point of the study was defined as time to complete ulcer healing. Participants receiving weekly application of EpiFix and compression were significantly more likely to experience complete wound healing than those receiving standard wound care and compression (60% versus 35% at 12 weeks, P = 0·0128, and 71% versus 44% at 16 weeks, P = 0·0065). A Kaplan-Meier analysis was performed to compare the time-to-healing performance with or without EpiFix, showing a significantly improved time to healing using the allograft (log-rank P = 0·0110). Cox regression analysis showed that subjects treated with EpiFix had a significantly higher probability of complete healing within 12 weeks (HR: 2·26, 95% confidence interval 1·25-4·10, P = 0·01) versus without EpiFix. These results confirm the advantage of EpiFix allograft as an adjunct to multilayer compression therapy for the treatment of non-healing, full-thickness venous leg ulcers.

Int Wound J. 2018 Dec;15(6):950-957. doi: 10.1111/iwj.12954. Epub 2018 Jul 17.
Use of an aseptically processed, dehydrated human amnion and chorion membrane improveslikelihood and rate of healing in chronic diabetic foot ulcers: A prospective, randomised, multi-centre clinical trial in 80 patients.
DiDomenico LA1, Orgill DP2, Galiano RD3, Serena TE4, Carter MJ5, Kaufman JP6, Young NJ7, Jacobs AM8, Zelen CM9.

Abstract
Amnion and chorion allografts have shown great promise in healing diabetic foot ulcers (DFUs). Results from an interim analysis of 40 patients have demonstrated the accelerated healing ability of a novel aseptically processed, dehydrated human amnion and chorion allograft (dHACA). The goal of this study was to report on the full trial results of 80 patients where dHACA was compared with standard of care (SOC) in achieving wound closure in non-healing DFUs. After a 2-week screening period, during which patients with DFUs were unsuccessfully treated with SOC, patients were randomised to either SOC alone or SOC with dHACA applied weekly for up to 12 weeks. At 12 weeks, 85% (34/40) of the dHACA-treated DFUs healed, compared with 33% (13/40) treated with SOC alone. Mean time to heal within 12 weeks was significantly faster for the dHACA- treated group compared with SOC, 37 days vs 67 days in the SOC group (P=.000006). Mean number of grafts used per healed wound during the same time period was 4.0, and mean cost of the tissue to heal a DFU was $1771. The authors concluded that aseptically processed dHACA heals DFUs significantly faster than SOC at 12 weeks.

J Am Podiatr Med Assoc. 2018 Mar;108(2):84-89. doi: 10.7547/17-039.
Use of Dehydrated Human Amnion/Chorion Membrane Allografts in More Than 100 Patients with Six Major Types of Refractory Nonhealing Wounds.
Garoufalis M, Nagesh D, Sanchez PJ, Lenz R, Park SJ, Ruff JG, Tien A, Goldsmith J, Seat A.

Abstract

BACKGROUND:
Biochemical properties of the amniotic membrane help modulate inflammation and enhance soft-tissue healing. In controlled trials, the efficacy of dehydrated human amnion/chorion membrane (dHACM) allografts has been established. Our purpose is to describe our experience with using dHACM to treat nonhealing wounds of various etiologies.

METHODS:
We conducted a retrospective review of deidentified data from 117 consecutive patients treated in an outpatient clinic with dHACM allografts with wounds of various etiologies over 2 years. The decision to use advanced wound-care treatments is based on rate of healing observed after initiation of standard wound care and patient risk factors. Eligibility for treatments such as amniotic membraneallografts includes wounds without 50% reduction after 4 weeks, or earlier in patients deemed to be at high risk for nonhealing or with a history of chronic wounds. In micronized or sheet formulation, dHACM is applied to the wound weekly after sharp/mechanical debridement as necessary, and wound-care practices appropriate for wound type and location are continued.

RESULTS:
Thirty-four percent of allograft recipients had diabetic foot ulcers, 25% had venous leg ulcers, 20% had surgical wounds, 14% had pressure ulcers, 6% had ischemic wounds, and 2% had traumatic wounds. Complete healing occurred in 91.1% of treated patients, with a mean ± SD number of weekly applications per healed wound of 5.1 ± 4.2.

CONCLUSIONS:
In addition to wounds of diabetic origin, dHACM can significantly expedite healing in refractory wounds of varying etiologies.

Int Wound J. 2019 Feb;16(1):19-29. doi: 10.1111/iwj.12976. Epub 2018 Aug 22.
A confirmatory study on the efficacy of dehydrated human amnion/chorion membrane dHACM allograft in the management of diabetic foot ulcers: A prospective, multicentre, randomised, controlled study of 110 patients from 14 wound clinics.
Tettelbach W1, Cazzell S2, Reyzelman AM3, Sigal F4, Caporusso JM5, Agnew PS6.

Abstract
A randomised, controlled multicentre clinical trial was conducted at 14 wound care centres in the United States to confirm the efficacy of dehydrated human amnion/chorion membrane allograft (dHACM) for the treatment of chronic lower extremity ulcers in persons with diabetes. Patients with a lower extremity ulcer of at least 4 weeks duration were entered into a 2-week study run-in phase and treated with alginate wound dressings and appropriate offloading. Those with less than or equal to 25% wound closure after run-in were randomly assigned to receive weekly dHACM application in addition to offloading or standard of care with alginate wound dressings, for 12 weeks. A total of 110 patients were included in the intent-to-treat (ITT) analysis, with n = 54 in the dHACM group and n = 56 in the no-dHACM group. Of the participants, 98 completed the study per protocol, with 47 receiving dHACM and 51 not receiving dHACM. The primary study outcome was percentage of study ulcers completely healed in 12 weeks, with both ITT and per-protocol participants receiving weekly dHACM significantly more likely to completely heal than those not receiving dHACM (ITT-70% versus 50%, P = 0.0338, per-protocol-81% versus 55%, P = 0.0093). A Kaplan-Meier analysis was performed to compare the time-to-healing performance with/without dHACM, showing a significantly improved time to healing with the use of allograft, log-rank P < 0.0187. Cox regression analysis showed that dHACM-treated subjects were more than twice as likely to heal completely within 12 weeks than no-dHACM subjects (HR: 2.15, 95% confidence interval 1.30-3.57, P = 0.003). At the final follow up at 16 weeks, 95% of dHACM-healed ulcers and 86% of healed ulcers in the no-dHACM group remained closed. These results confirm that dHACM is an efficacious treatment for lower extremity ulcers in a heterogeneous patient population.

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AP-011855B_02-Jul-2019