Beyond Clearance:

Understanding the Value of PMA in Advanced Wound Therapies

Supported by an educational grant from Organogenesis Inc.

Faculty

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Faculty Disclosures

- **Daniel L. Kapp, MD**
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- **Paula Pons, MD, CWSP**
  Nothing to disclose in relation to this activity

Disclosures

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  - Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
  - This activity has been independently reviewed for balance.

This continuing medical education activity includes device or medicine brand names for participant clarity purposes only. No product promotions or recommendations should be inferred.

Learning Objectives

- Describe the FDA Premarket Approval (PMA) process for skin substitutes, including key regulatory requirements and what PMA approval signifies regarding safety and efficacy
- Differentiate PMA-approved skin substitutes from other regulatory pathways, and discuss the clinical and practical implications of PMA status in wound care practice
- Evaluate the role of clinically proven PMA-approved products in improving patient outcomes, including how evidence-based product selection influences treatment decisions and quality of care

PMA = premarket approval.

Navigating the Skin Substitute Landscape: An Algorithmic Framework for Patient and Product Selection and Reimbursement

Daniel L. Kapp, MD
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There Are Four Pathways to Commercialization

- 361 PHSA
  - Permits the FDA to allow marketing of human tissues, provided that it is
    - Minimally manipulated
    - Homologous use

- 510(k) FD&C Act
  - Permits the FDA to allow marketing of device, provided that it is
    - Substantially equivalent
      - Safety
      - Effectiveness
    - to a legally marketed Predicate Device

PHSA = Public Health Service Act; FD&C = Food, Drug, and Cosmetics.

The U.S. Food and Drug Administration (FDA). Accessed April 6, 2026. https://www.fda.gov/media/109176/download; https://www.fda.gov/media/162539/download.

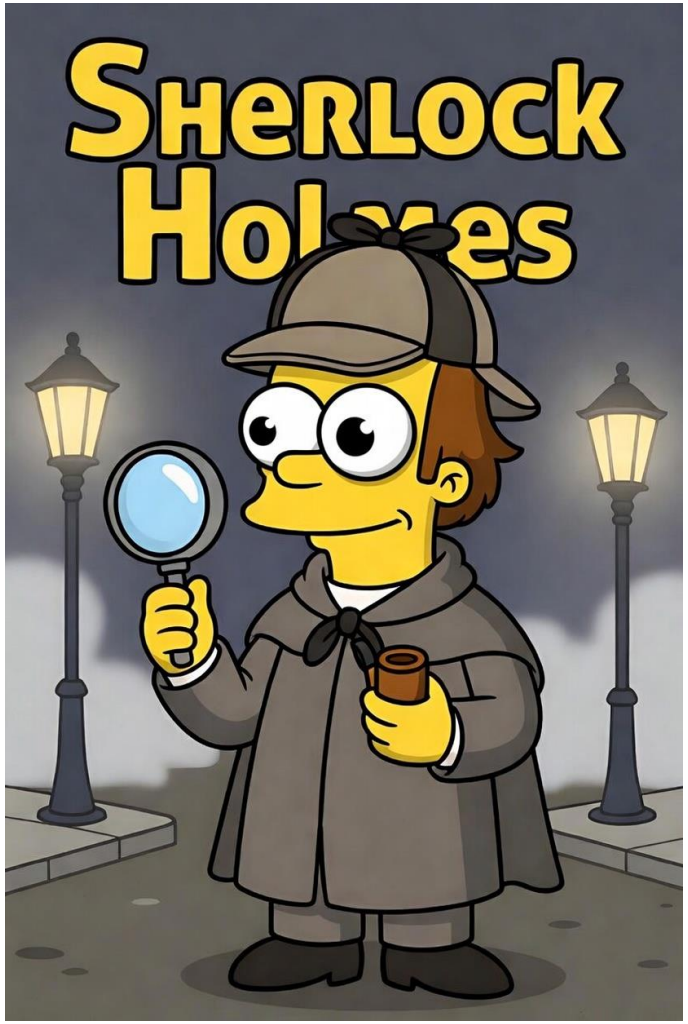
There Are Four Pathways to Commercialization

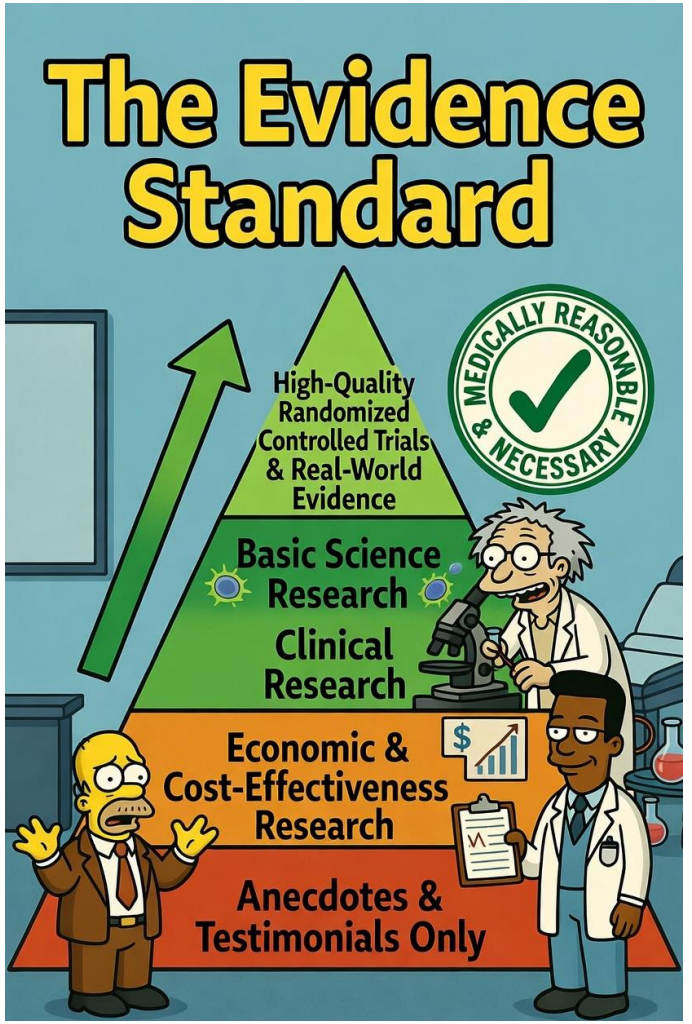
- PMA of the FD&C Act
  - For *de novo* technology
  - For high-risk devices (class III)
  - Requires a stringent study
- Section 351 PHSA
  - Regulation of complex biological products, such as
    - Vaccines, blood products, and advanced cellular therapies
  - Requires Biologics License Application (BLA) to prove safety, purity, and potency

BLA = biologics license application.

FDA. Accessed April 6, 2026. https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma; https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biologics-license-applications-bla-process-cber.

Bridging the Critical Gap





What Is the Evidence Burden by Pathway?

Pathway	Primary Standard	Human Trials?	Typical Level of Evidence
Section 361 (HCT/P)	Disease Prevention	No	Donor screening, tissue testing, CGTP compliance
510(k) Clearance	Substantial Equivalence	Rarely (~10%)	Bench testing, biocompatibility, animal models
PMA	Safety and Effectiveness	Yes	Valid Scientific Evidence (VSE), massive RCTs
Section 351 (Biologic)	Safe, Pure, and Potent	Yes	IND to BLA: Phase 1, 2, and 3 clinical trials

HCT/P = human cells, tissues, and cellular and tissue-based products; CGTP = current good tissue practice; VSE = valid scientific evidence; RCTs = randomized controlled trials; IND = investigational new drug application.

This Is Heavy Stuff: A Wound Joke

Did you hear about the shipment of bandages that was hijacked?

Probably not because the police are keeping it under wraps.

Section 361: Zero Clinical Data

The Standard

The evidence submitted to the FDA has nothing to do with efficacy. The focus is strictly on communicable disease control and preventing transmission.

What Must Be Proven

Manufacturers must prove compliance with Current Good Tissue Practices (CGTPs), including donor screening and validated cleanroom manufacturing.

The Commercial Trap

Because the FDA requires zero clinical evidence, companies often launch without it. Consequently, Medicare (CMS) frequently denies coverage.

CGTPs = current good tissue practices; CMS = Centers for Medicare and Medicaid Services.

FDA. Accessed April 6, 2026. https://www.fda.gov/media/109176/download.

The Boundaries of Section 361

Minimal Manipulation

For structural tissue, processing cannot alter the original relevant characteristics relating to its utility for reconstruction or repair.

Example: You can clean, size, and freeze it. However, if you decellularize it so aggressively that it loses its physical integrity, or grind it into a paste, you have altered its original characteristics.

Homologous Use

The repair, reconstruction, or replacement with an HCT/P that performs the same basic function in the recipient as in the donor.

Example: Using an amniotic membrane to cover a wound works because its native function is serving as a barrier. Using amniotic fluid to treat joint pain is non-homologous.

FDA. Accessed April 6, 2026. https://www.fda.gov/media/109176/download.

510(k): Bench and Animal Pathway

- Substantial Equivalence
  - ***In Vitro* (Bench Testing)**: Mechanical strength, degradation profiles, porosity, and barrier function assessments
  - **Biocompatibility**: ISO 10993 testing (cytotoxicity, sensitization, irritation) to prove the material is non-toxic
  - ***In Vivo* (Animal Models)**: Often required for newer matrices to show integration, vascularization, and lack of adverse response

ISO = International Organization for Standardization.
FDA. Accessed April 6, 2026. https://www.fda.gov/media/162539/download.

Premarket Approval (PMA)

Valid Scientific Evidence

VSE

Standalone Proof Required

- For Class III devices lacking a predicate, the FDA requires “Valid Scientific Evidence”
- This represents a massive barrier to entry
- It demands exhaustive pre-clinical bench testing combined with statistically powered, randomized controlled clinical trials (RCTs) proving standalone safety and effectiveness over a control group

FDA. Accessed April 6, 2026. https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma.

Section 351

The Pharmaceutical Standard

- If a cellular or tissue product is more than minimally manipulated or intended for non-homologous use, it falls into the 351 pathway
- The product must be proven to be “safe, pure, and potent”
  - This mirrors the evidentiary burden of new pharmaceutical drugs, requiring an IND application followed by Phase 1, Phase 2, and Phase 3 clinical trials before a BLA is granted

FDA. Accessed April 6, 2026. https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biologics-license-applications-bla-process-cber.

FDA vs CMS: Two Languages

- **FDA Mandate:** Is it *Safe and Effective*? This determines clearance/approval to legally sell the product
- **CMS Mandate:** Is it *Reasonable and Necessary*? This determines willingness to pay (reimbursement)
- **The E&I Trap:** The paradox of the pathway—when it requires no clinical data for the FDA
  - Consequently, CMS routinely denies coverage citing them as “Experimental and Investigational”
- **The Solution:** Peer-reviewed clinical literature (RCTs) is required to overcome the E&I designation, effectively forcing trials anyway

E&I = experimental and investigational.

Time for a Dad Joke

What do you call a dad joke about an 85-year-old female with a 14-year history of prednisone for polymyalgia rheumatica and venous insufficiency who has a nonhealing wound after lacerating her leg on a dishwasher door?

Answer

- R46.89 Weird
- R46.2 Inexplicable Behavior
- Y07.11 Father Perpetrator
- S81.811D Laceration Leg
- W22.8XXD Striking an Object
- W29.0 Powered Home Appliance
- I87.2 Venous Insufficiency
- M35.3 PMR
- Z79.52 Long-Term Steroid Use

PMR = partial metabolic response.

Time to Market vs Evidence

Estimated months to market authorization. The immense time and cost gap between 361/510(k) and PMA/351 is driven entirely by the burden of producing Phase 3 human clinical evidence.

Sexton ZA, et al. *JAMA Health Forum*. 2023;4(8):e232260.

How the FDA Defines Safety

Safety Is a Calculus, Not an Absolute

- **The Misconception**: “Safe” means “harmless” or “zero risk”
- **The FDA Definition**: Safety is established when a drug’s benefits outweigh its known and potential risks for the intended population
- **Evidence Required**
  - **Pre-clinical**: Animal toxicology models
  - **Phase I Trials**: Testing in healthy volunteers to establish maximum tolerated doses
  - **Adverse Event (AE) Monitoring**: Continuous tracking of adverse effects

AE = adverse event.

FDA. Accessed April 6, 2026. https://www.fda.gov/media/164563/download. All Clinical Trials. Accessed April 6, 2026. https://www.allclinicaltrials.com/blog/what-are-virtual-clinical-trials.

Efficacy vs Effectiveness

Feature	Efficacy (“Can it work?”)	Effectiveness (“Does it work?”)
Setting	Highly controlled, ideal clinical conditions	Real-world, diverse clinical practice
Population	Strict inclusion/exclusion criteria (often excludes comorbidities)	Diverse patient populations, varying ages, overlapping diseases
Adherence	Closely monitored, extremely high compliance	Natural patient behavior (missed doses, incorrect timing)
Study Type	Phase II and III RCTs	Phase IV Surveillance, Pragmatic Trials, Real-World Evidence (RWE)

RWE = real-world evidence.

Gartlehner G, Hansen RA, Nissman D, et al. Technical Reviews. No 12. Agency for Healthcare Research and Quality (US); 2006.

The Continuum of Clinical Evidence

Proving Safety

Relies on pre-clinical data, Phase I safety profiles, and lifelong post-market surveillance. Safety is an ongoing, dynamic assessment.

Proving Efficacy

Established through double-blind, placebo-controlled Phase III trials. This is the gold standard required for initial FDA approval.

Proving Effectiveness

Demonstrated via Electronic Health Record (EHR) mining, patient registries, and observational studies over years of general public use.

EHR = electronic health record.

Gartlehner G, Hansen RA, Nissman D, et al. Technical Reviews. No 12. Agency for Healthcare Research and Quality (US); 2006.

Number Needed to Treat

The Metric

The **Number Needed to Treat (NNT)** is the number of patients you need to treat with the intervention to prevent exactly *one* additional bad outcome.

$$\mathrm{NNT} = \frac{1}{\mathrm{ARR}}$$

Where ARR is Absolute Risk Reduction: the difference in risk between the control group and the treatment group.

Clinical Interpretation

The Ideal Scenario: An NNT of 1 means every single patient treated benefits directly from the intervention.

The Reality: Lower is always better. An NNT of 5 is fantastic in clinical practice.

The Warning: An NNT of 100 means 99 people take the drug with no added benefit to prevent 1 bad event. A drug might have a “statistically significant” effect, but if the NNT is 500, it might not be clinically worthwhile given the cost and adverse effects.

NNT = number needed to treat; ARR = absolute risk reduction.

Other Key Terms

PAR (Percent Area Reduction)

A critical metric measuring the percentage decrease in wound area over a specific time. PAR is often used as a strong early predictor of ultimate complete wound healing.

TTC (Time to Closure)

The total duration measured in days or weeks from the initiation of treatment until the wound achieves complete, 100% epithelialization without drainage.

P-Value

A statistical measurement indicating the probability of obtaining test results by chance. A P-value of <.05 is generally considered statistically significant in clinical trials.

Randomness (in RCTs)

The process of randomly assigning participants to treatment or control groups. This eliminates selection bias, ensuring that the groups are comparable and outcome differences are valid.

PAR = percent area reduction; TTC = time to closure.

Premarketing vs Postmarketing

Premarketing Studies (RCTs)

- Studies conducted to establish safety and efficacy required for FDA approval
- These are typically prospective, Randomized Controlled Trials (RCTs) characterized by
  - Strict inclusion/exclusion criteria
  - Highly controlled clinical environments
  - Randomized patient allocation to prevent bias
  - Focus on proving efficacy over standard care

Postmarketing Studies (RWE)

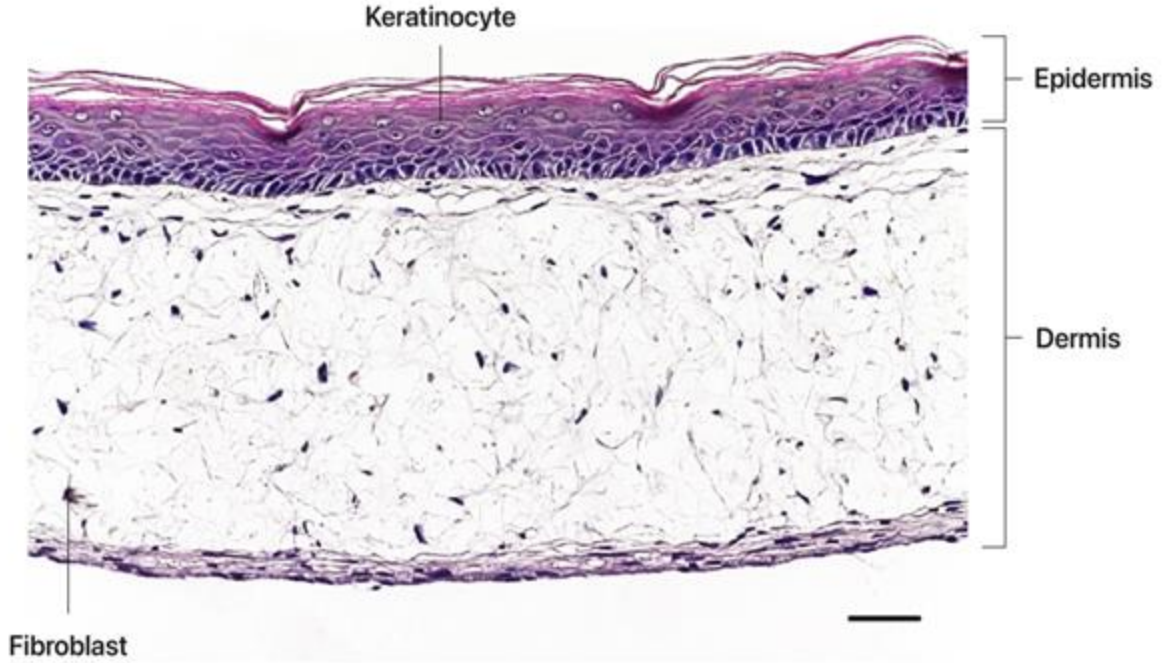
- Observational studies evaluating how a product performs in routine, everyday clinical practice after approval
- Real-World Evidence (RWE) is characterized by
  - Broad, diverse patient populations
  - Analysis of large electronic medical record (EMR) datasets
  - Comparative effectiveness against competing therapies
  - Evaluation of real-world utilization and outcomes

Li LY, et al. *Clin Trials*. 2026:17407745251415190. [Epub ahead of print.]

Mechanism of Action

Bioengineered bilayered living cell therapy consisting of human neonatal epidermal keratinocytes and dermal fibroblasts suspended in a bovine type I collagen matrix.

- **Active Cytokine Expression:** Acts as an active biological engine rather than just a scaffold. Living cells express a robust profile of cytokines and growth factors.
- **Reversing Chronicity:** Releases fibrogenic and angiogenic signals into the wound bed, transitioning the wound out of a stalled, chronic inflammatory state.
- **Host Stimulation:** “Jump-starts” host tissue, stimulating the patient’s own cells to migrate, proliferate, and synthesize new matrix and blood vessels.



Zaulyanov L, Kirsner RS. *Clin Interv Aging*. 2007;2(1):93-98. Kolundzic N. October 31, 2024. Updated January 15, 2026. Accessed April 6, 2026. https://www.reprocell.com/blog/biopta/reprocells-advanced-skin-tissue-engineering.

Pivotal Study for VLU

293

Total Patients Enrolled

LBLSS + Compression vs Standard Care

This prospective, randomized, controlled multicenter trial demonstrated that treatment with Graftskin (LBLSS) was significantly more effective than compression therapy alone.

63%

Complete Closure (LBLSS)

49%

Complete Closure (Control)

61 Days

Median TTC (LBLSS)

181 Days

Median TTC (Control)

VLU = venous leg ulcer; LBLSS = layered bilayered living skin substitute.

Falanga V, et al. *Arch Dermatol*. 1998;134(3):293-300.

Pivotal Study for DFU

208
Total Patients Enrolled

LBLSS + Standard Care vs Control

Evaluated LBLSS combined with standard diabetic foot care vs standard care (saline-moistened gauze) alone over a 12-week primary endpoint.

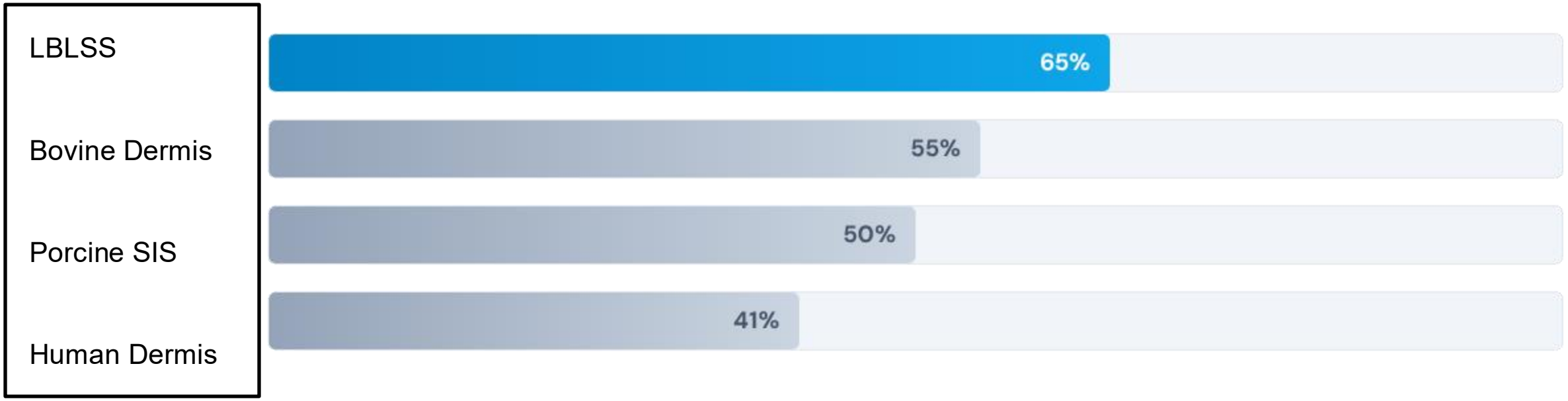
56% Complete Closure (LBLSS)	**38%** Complete Closure (Control)
65 Days Median TTC (LBLSS)	**90 Days** Median TTC (Control)

DFU = diabetic foot ulcer.

Veves A, et al. *Diabetes Care*. 2001;24(2):290-295.

Postmarketing Study: Comparative Effectiveness

Retrospective observational studies using large electronic medical record (EMR) databases have evaluated how LBLSS performs in routine clinical practice compared with other products.



SIS = small intestinal submucosa.

Marston WA, et al. *Wound Repair Regen*. 2014;22(3):334-340. Treadwell T, et al. *Adv Wound Care (New Rochelle)*. 2018;7(3):69-76. Sabolinski ML, et al. *J Comp Eff Res*. 2018;7(8):797-805.

Real-World Evidence: DFU

In a prominent comparative effectiveness study matching LBLSS vs amniotic membrane (AM) for DFUs, LBLSS demonstrated superior healing outcomes.

- **Incidence of Closure (12 Weeks):**
  48% for LBLSS vs 28% for AM.

- **Speed of Healing:**
  LBLSS was shown to close DFUs 49% faster.

- **Median Time to Closure:**
  13 weeks for LBLSS compared to 26 weeks for AM.

AM = amniotic membrane.
Kirsner RS, et al. *Wound Repair Regen*. 2015;23(5):737-744.

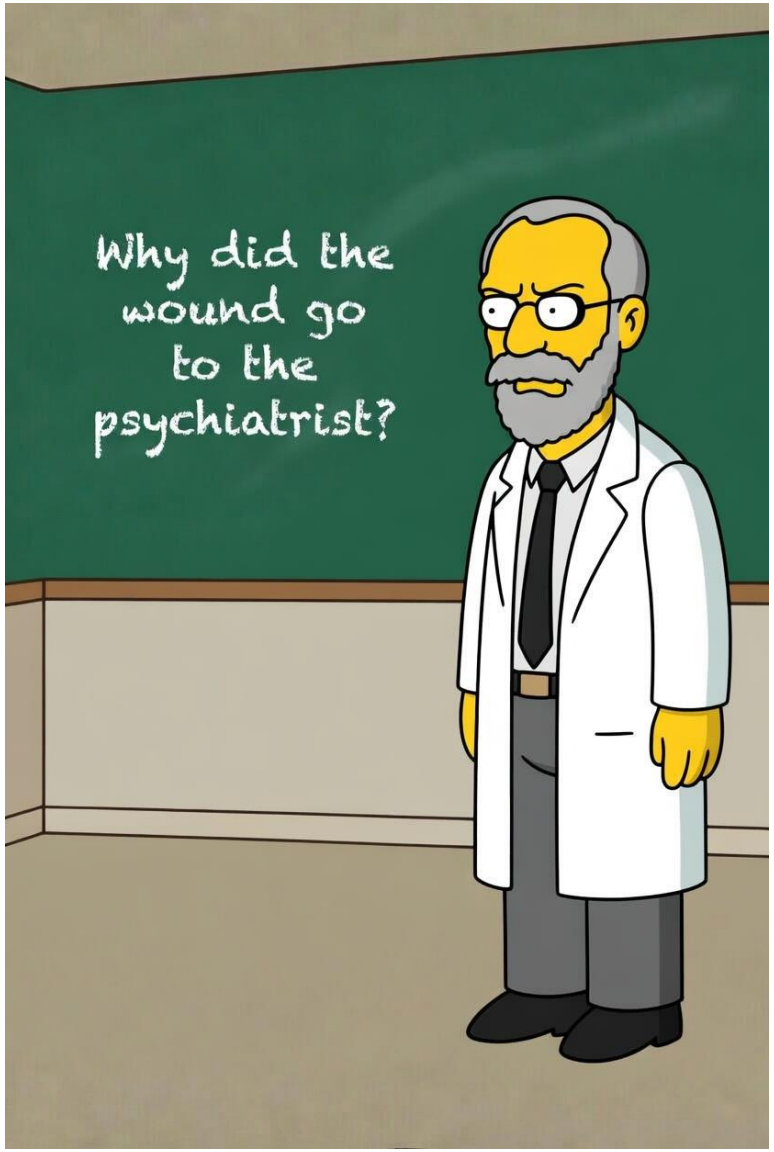
The Final Analysis: Health Economics

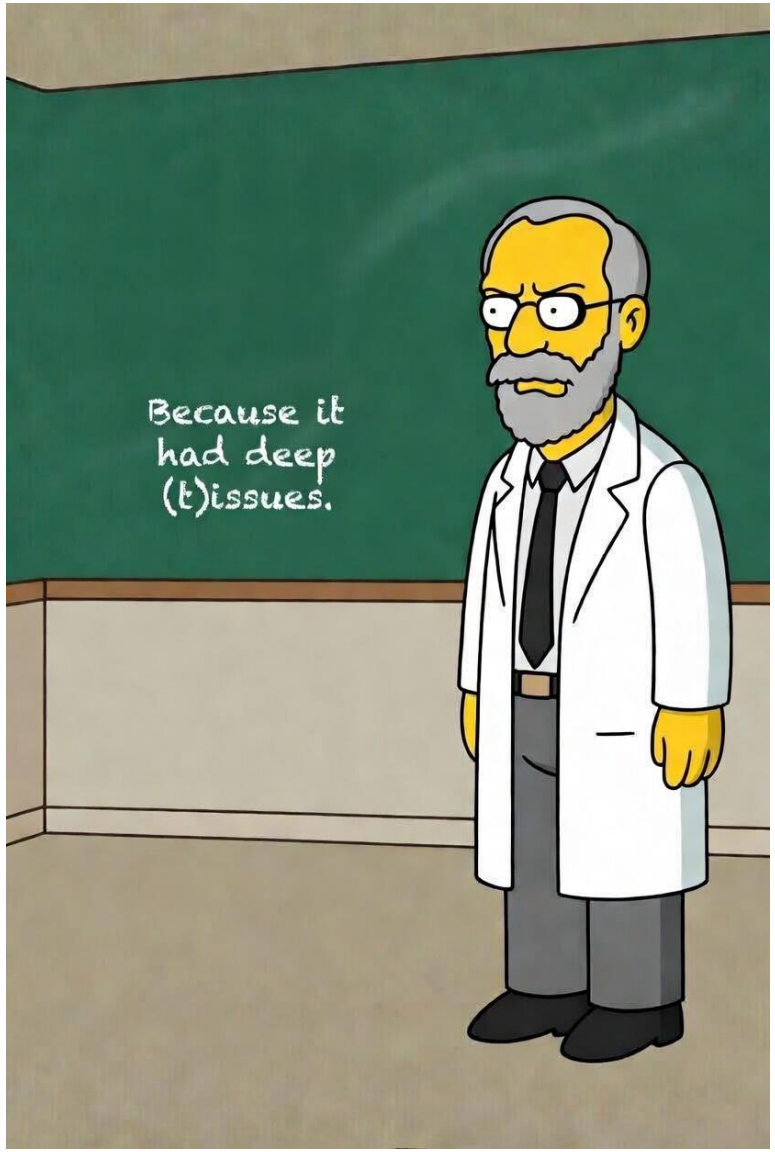
While advanced skin substitutes carry a higher initial product cost, retrospective claims analyses and economic models demonstrate

- **28% Reduction in Amputations:** Over an 18-month follow-up period, patients treated with LBLSS had significantly fewer lower limb amputations.
- **33% Fewer Hospitalized Days:** Accelerated healing translates to fewer severe complications and reduced inpatient care requirements.
- **$5253 Cost Reduction:** Overall, this equated to an average per-patient healthcare cost reduction of over $5000 USD.

Rice JB, et al. *J Med Econ.* 2015;18(8):586-595.

The Final Dad Joke





Clinical Pearls: What a Provider Must Know

- Providers uniquely span both care delivery and evidence interpretation
- Understand and apply the data that validates
  - Safety: Benefits outweigh risks
  - Efficacy: Proven in controlled clinical trials
  - Effectiveness: Demonstrated in real-world practice
- By aligning clinical expertise with scientific evidence, providers bridge the divide between FDA authorization and CMS reimbursement, ensuring therapies are reasonable, necessary, and reimbursable

The Role of Clinically Proven PMA-Approved Products in Improving Patient Outcomes

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Paula Pons Physician, LLC
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What Does This Mean for My Clinical Practice?

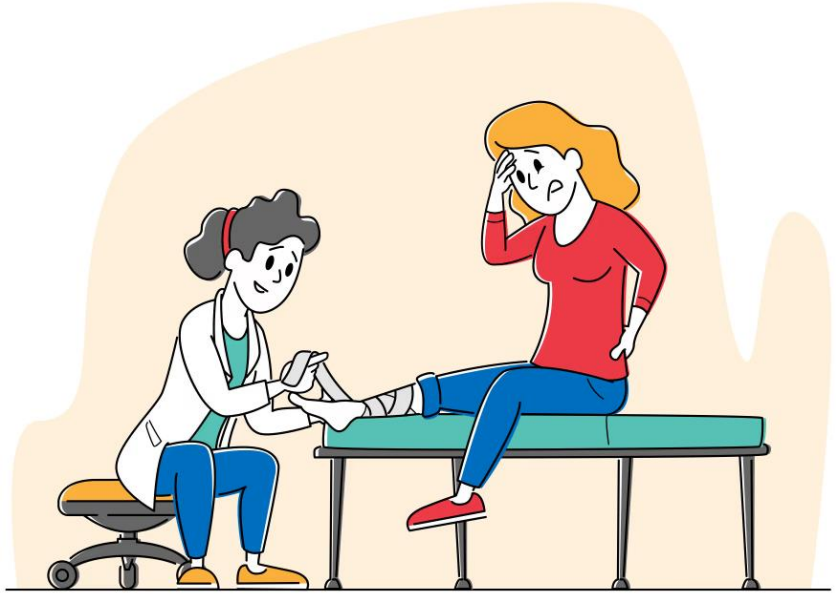
- **PMA Skin Substitutes**
  - Undergo far more rigorous FDA review
  - Require clinical evidence of safety and effectiveness
  - Historically align with higher, device-oriented reimbursements

- **510(k) Substitutes**
  - Only need to show substantial equivalence to a predicate device, meaning less evidence, lower regulatory burden, and often lower reimbursement

The FDA Group. Accessed April 1, 2026. https://www.thefdagroup.com/blog/pma-vs-510k.

Clinical Advantages of PMA Skin Substitutes

- **Stronger clinical evidence**
  - PMA products must show **actual wound-healing outcomes**, not just equivalence
  - This can translate to **more predictable healing trajectories** and **better support for medical necessity**
- **Higher assurance of safety**
  - PMA review includes **manufacturing validation**, sterility assurance, and long-term safety data
- **Better support in audits**
  - When payers or auditors question utilization, PMA-level evidence provides stronger justification



Song EH and Hamm T. WoundReference. Updated March 18, 2026. Accessed April 1, 2026. https://woundreference.com/p/blog?id=skin-substitutes---whats-new-in-2026-frequently-asked-questions.

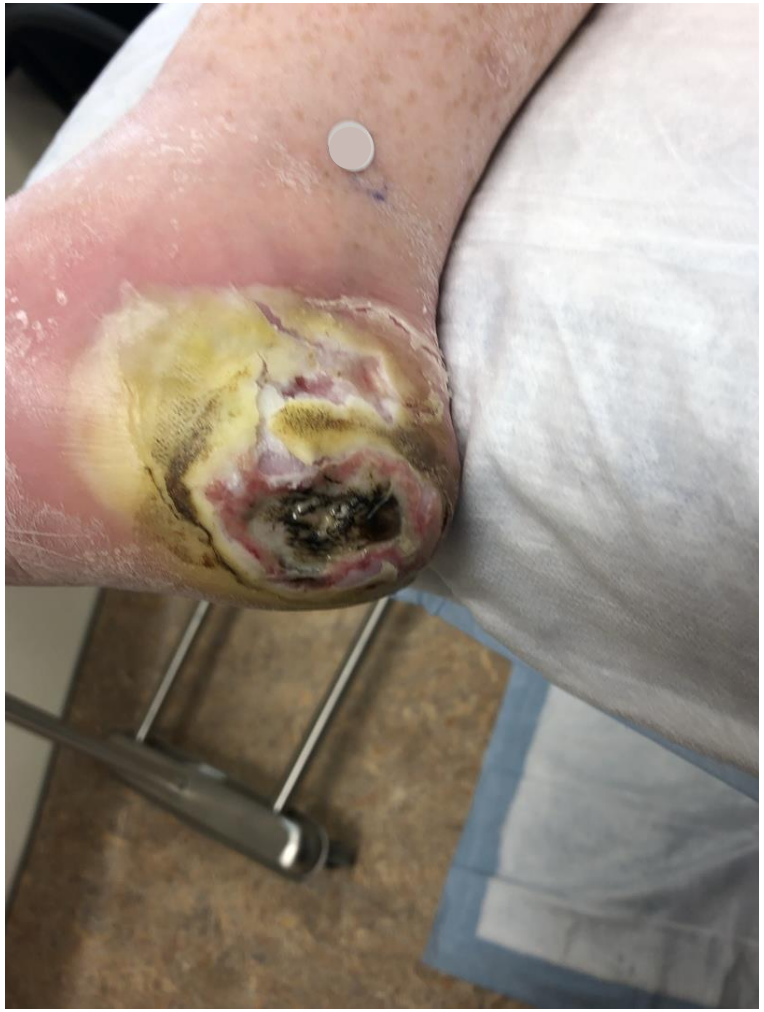
Operational and Compliance Advantages of PMA Products

- **Lower risk of misclassification or denial**
  - Payers increasingly scrutinize skin substitute use
  - PMA products' evidence and regulatory rigor reduce risk of
    - Medical necessity denials
    - Coding disputes
    - Post-payment recoupments
- **Stronger alignment with CMS documentation expectations**
  - CMS emphasizes linking product choice to clinical evidence
  - PMA products inherently support this

Song EH and Hamm T. WoundReference. Updated March 18, 2026. Accessed April 1, 2026. https://woundreference.com/p/blog?id=skin-substitutes---whats-new-in-2026-frequently-asked-questions.

Case 1

- 50-year-old Female presents with a heel ulcer of 9 weeks duration
- Ulcer appeared after she started using a new brace for foot drop
- Ulcer size on admission: 6 cm^2
- Type 2 DM, HbA1c 8.3%
- History of PAD
  - Had angioplasty and stent placement x 2 (ATA and PTA)
- Works as a middle school teacher (now on summer break)
- Very supportive family structure

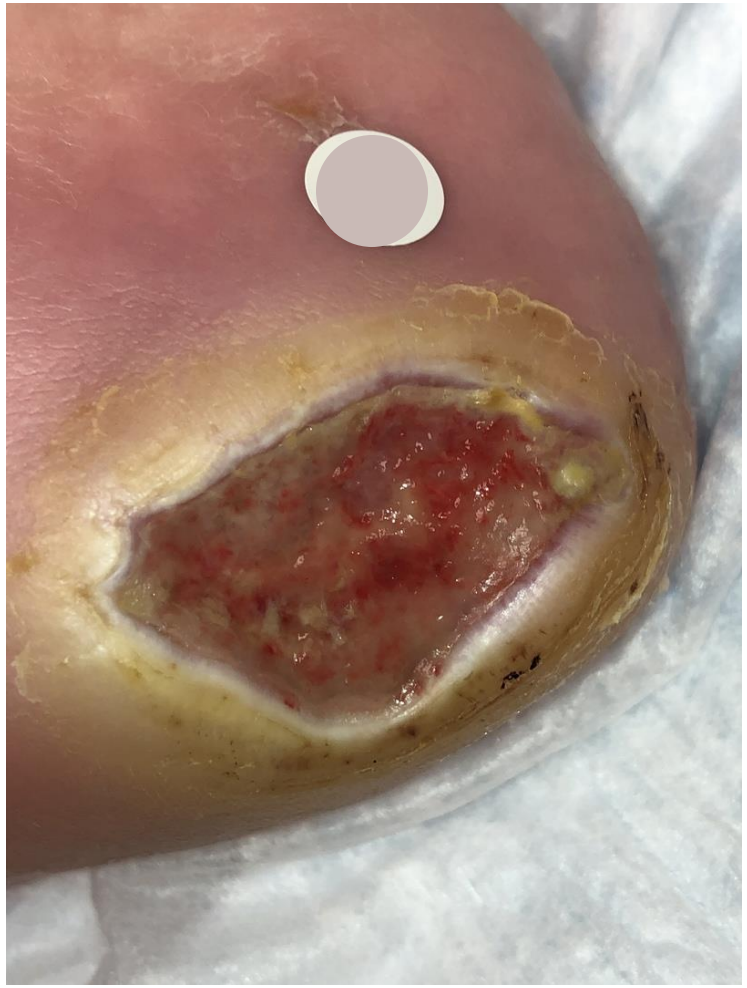


First visit

DM = diabetes mellitus; PAD = peripheral artery disease; ATA = anterior tibial artery; PTA = posterior tibial artery.

Conventional Wound Therapy

- Weekly follow-ups
- Serial debridement
- MRSA wound infection treated with systemic antibiotics and silver alginate for bioburden control
- No deep infection, no osteomyelitis
- Pressure relief with total contact cast
- Working with diabetic educator to optimize diet
- Week 7
  - Stalled (no measurable signs of improvement)
  - Good granulation
  - No signs/symptoms of infection

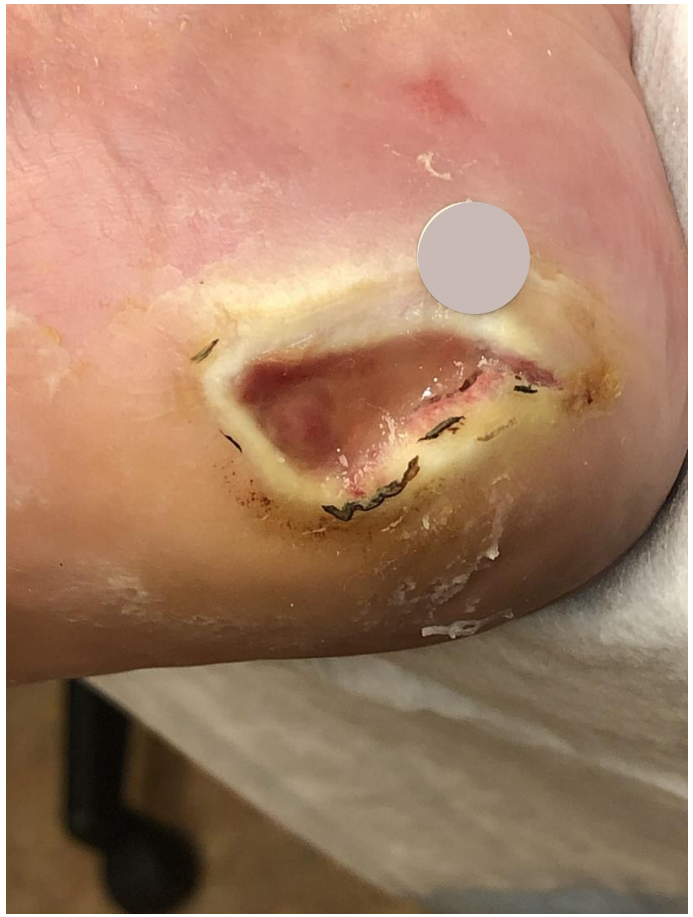


Week 7

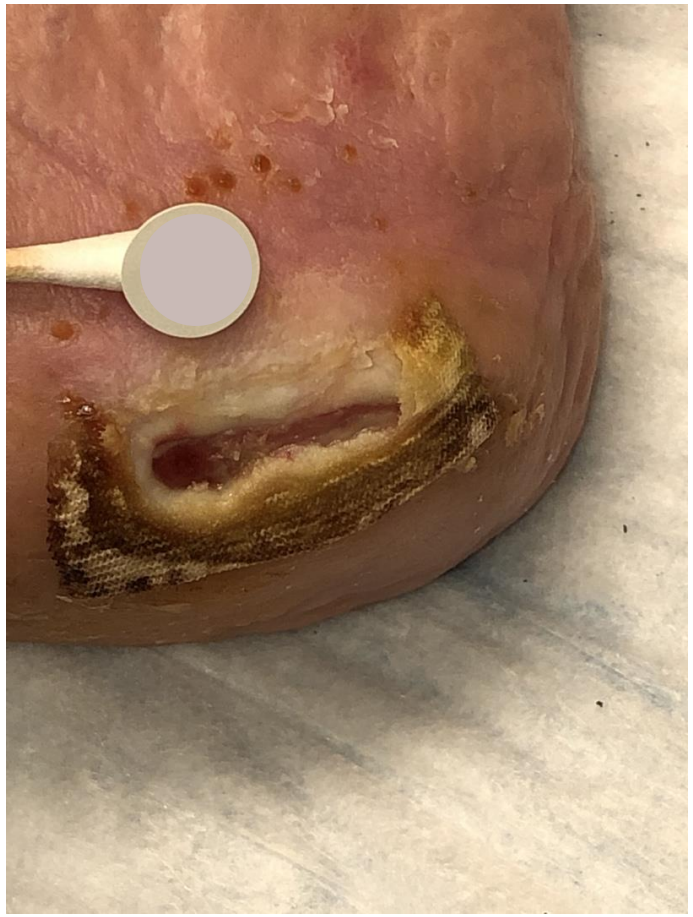
MRSA = methicillin-resistant *Staphylococcus aureus*.

Advanced Wound Therapy with PMA Skin Substitute

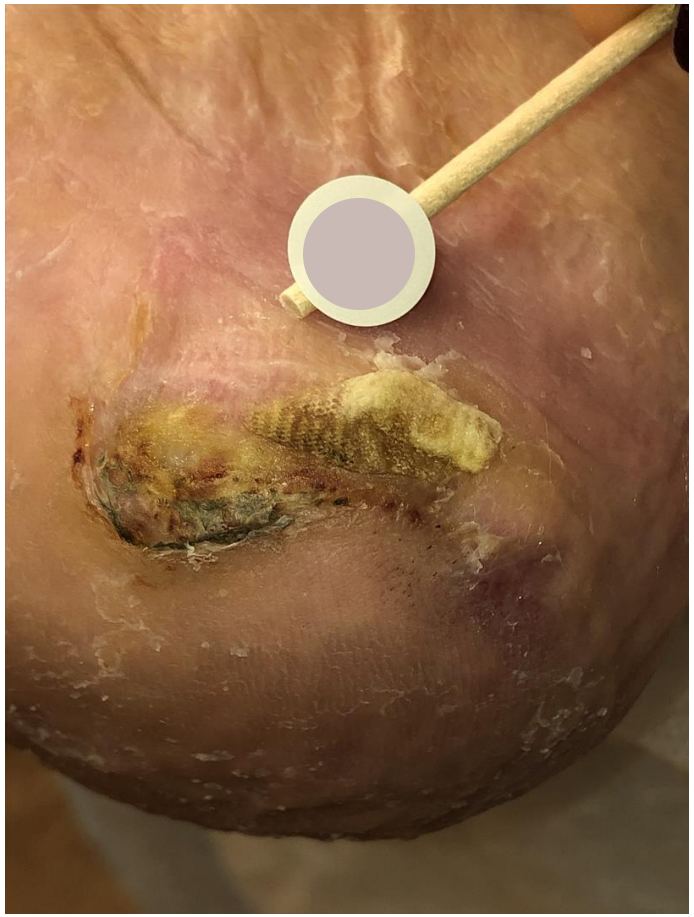
Adding a PMA Skin Substitute (BLCC) healed the ulceration with 5 applications



Week 8



Week 11



Week 14

BLCC = bilayered living cellular construct.

Why We Chose a PMA Skin Substitute

- Data shows that the percentage change in wound area over a 4-week period is a robust predictor of complete healing at 12 weeks
- Our patient had shown improvement in the quality of the tissue, with no improvement in measurements
- Risk factors at the first visit affecting her odds of healing included wound size and duration
- Patient with diabetes at high risk for complications
  - Resolved infection but at risk for recurrence
  - The PMA Skin Substitute used in this patient, BLCC, is proven to lower the incidence of osteomyelitis and amputations
- Looking to heal ASAP in order to have the brace revised and be back to work for the beginning of the school year
- Using a PMA Skin Substitute gave me the most predictable healing trajectory and gave the patient the highest chance of healing her wound in an expected time frame

Sheehan P, et al. *Diabetes Care*. 2003;26(6):1879-1882. Margolis DJ, et al. *Diabet Med*. 2005;22(2):172-176. Margolis DJ, et al. *Am J Med*. 2003;115(8):627-631. Veves A, et al. *Diabetes Care*. 2001;24(2):290-295

Case 2

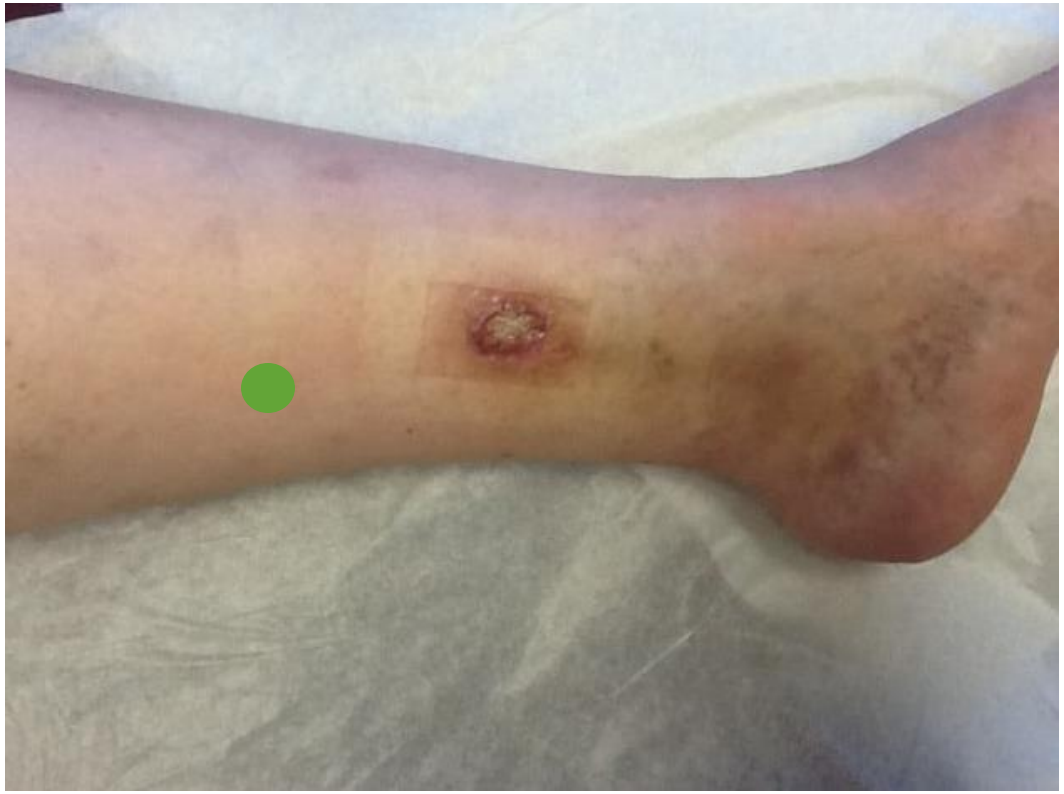
- 62yo Female presents with a venous leg ulcer of 7 months duration
- She first noticed her ulcer while showering
- No history of trauma
- Ulcer measured 3 cm^2
- Moderate serous fluid drainage
- Reports bilateral lower leg edema, L>R, that improves with elevation and after sleeping in bed
- Does not wear compression
- ABI: 0.8
- History of left knee replacement 2 years ago

- Ulcer was treated with conventional wound therapy for 4 weeks
  - Serial debridement
  - Alginate dressings to achieve moisture control
  - 3-layer compression bandages for edema control
- No signs/symptoms of infection
- Referral for venous reflux study

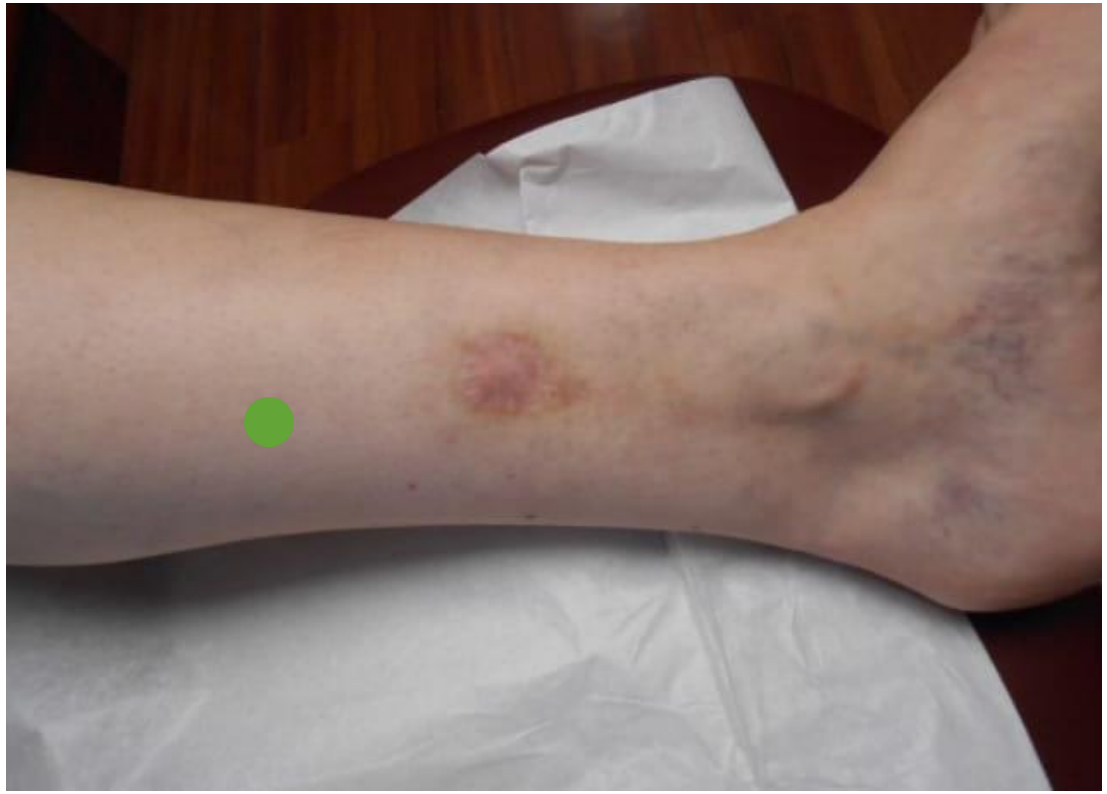
ABI = ankle-brachial index.

Advanced Wound Therapy with PMA Skin Substitute

- By week 5, wound was stalled (2.7 cm^2) despite adherence with wound care, edema control, and no infection
- Addition of PMA Skin Substitute healed the ulcer in 4 applications



Week 4



Week 9

Why We Chose a PMA Skin Substitute

- Data shows that percentage change in area from baseline to week 4 is a good predictor of healing at 24 weeks
- This patient's ulcer had only 10% decrease in area from baseline to week 4
- There are risk factors associated with failure of a VLU to heal
- Our patient had a prior total knee replacement, and her ulcer had been present for 7 months and was at the ankle
- Odds were against her ulcer healing with conventional wound therapy
- We chose a PMA Skin Substitute, BLCC, that has proven to heal the more of the most difficult VLUs in the shortest time, has real-world data, and a mechanism of action that changes the gene expression in VLUs

VLU = venous leg ulcer.

Kantor J, Margolis DJ. *Br J Dermatol.* 2000;142(5):960-964. Margolis DJ, et al. *Arch Dermatol.* 1999;135(8):920-926. Marston WA, et al. *J Vasc Surg Venous Lymphat Disord.* 2017;5:829-835.e1. Stone RC, et al. *Sci Transl Med.* 2017;9(371):eaaf8611. Stone RC, et al. *Wound Repair Regen.* 2020;28(2):164-176

Summary

Feature	PMA Skin Substitutes	510(k) Skin Substitutes
FDA Risk Class	Class III	Class II
Evidence Required	**Clinical trials, safety, and effectiveness data**	Bench testing; **no clinical trials required**
Regulatory Scrutiny	**Highest**	Moderate
Predictability of Outcomes	**Highest (evidence-based)**	Variable
Audit/Compliance Strength	**Strong**	Moderate
Historical Reimbursement	**Higher (ASP/device-oriented)**	Lowest (supply-oriented)
Future CMS Payment Position	**Likely favorable**	Less favorable

ASP = average sales price.

U.S. Food and Drug Administration. Accessed April 1, 2026. https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma; https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k.

Bottom Line for a Practicing Clinician

Questions?

Thank You!