



American Burn Association

625 N. Michigan Avenue, Ste. 1530
Chicago, Illinois 60611

Voice (312) 642-9260
(800) 548-2876

Fax (312) 642-9130
e-mail: info@ameriburn.org

4427 00 AUG 28 19:10

August 25, 2000

PRESIDENT

Ronald G. Tompkins, MD, ScD
GRB 1302
Massachusetts General Hospital
55 Fruit Street
Boston, Massachusetts 02114
(617) 726-3447

PRESIDENT-ELECT

Jeffrey R. Saffle, MD
Department of Surgery, Room 3B306
Univ. of Utah School of Medicine
50 North Medical Drive
Salt Lake City, Utah 84132
(801) 581-4490

FIRST VICE-PRESIDENT

John F. Hansbrough, MD
Department of Surgery, 8896
Univ. of California, San Diego Medical Center
200 West Arbor Drive
San Diego, California 92103
(619) 294-6042

SECOND VICE-PRESIDENT

Daniel L. Traber, PhD
Shriners Hospitals for Children
815 Market Street
Galveston, Texas 77550
(409) 772-6405

SECRETARY

Richard L. Gamelli, MD
Loyola University Medical Center
2160 S. First Avenue
Maywood, Illinois 60153
(708) 327-2444

TREASURER

Gary F. Purdue, MD
Department of Surgery
Univ. of Texas Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75235
(214) 648-2041

PROGRAM CHAIR

Lynn D. Solem, MD
Regions Hospital
640 Jackson Street
St. Paul, Minnesota 55101
(651) 221-2810

AT-LARGE MEMBERS

Rosie Thompson, RN, MS
Univ. of Kansas Medical Center
3901 Rainbow Blvd.
Kansas City, Kansas 66160
(913) 588-6539

Mary Gordon, RN, MS
Shriners Hospitals for Children
815 Market Street
Galveston, TX 77550
(409) 770-6904

Michele Gottschlich, PhD, RD
Shriners Hospitals for Children
3229 Burnet Avenue
Cincinnati, Ohio 45229
(513) 872-6298

PAST PRESIDENTS

John L. Hunt, MD
Department of Surgery
Univ. of Texas Southwestern Medical Center
5323 Harry Hines Blvd.
Dallas, Texas 75235
(214) 648-2152

Cleon W. Goodwin, MD
U.S. Army Institute of Surgical Research
3400 Rawley E. Chambers Ave.
San Antonio, Texas 78234
(210) 916-2720

Edwin A. Deitch, MD
UMD-New Jersey Medical School
Department of Surgery
185 South Orange Avenue, Room G-506
Newark, New Jersey 07103
(973) 972-5045

Executive Director

John A. Krichbaum, JD

Senior Director

Susan M. Browning, MPH

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**RE: Draft Guidance for Industry on Chronic Cutaneous
Ulcer and Burn Wounds—Developing Products for
Treatment**

Dear Sir or Madam:

I am writing on behalf of the American Burn Association in response to the FDA Draft Guidance for Industry on Chronic Cutaneous Ulcer and Burn Wounds.

The American Burn Association (ABA) was founded in 1967 following a series of annual seminars sponsored by leading institutions in the field of burn treatment. Today, it is a major multi-disciplinary professional organization, with over 3,500 members representing virtually every segment of burn care, research, rehabilitation, prevention, and teaching.

We believe that the Draft Guidance document is relatively thorough. Our only recommendation is that this Guidance document should be consistent with the standards currently under development by the American Society for Testing and Materials (ASTM) for Tissue Engineered Medical Products (see enclosed).

We would be happy to work with you further as you finalize the Guidance for Industry document. Should you need any further information, please feel free to contact John A. Krichbaum of the ABA Central Office at (312) 642-9260.

Thank you for the opportunity to comment on this important issue.

Sincerely,

Richard Kagan, MD, FACS
Chair, ABA Government Affairs Committee

DRAFT STANDARD

SKIN ASSESSMENT

THIS DOCUMENT IS NOT AN ASTM STANDARD; IT IS UNDER CONSIDERATION WITHIN AN ASTM TECHNICAL COMMITTEE BUT HAS NOT RECEIVED ALL APPROVALS REQUIRED TO BECOME AN ASTM STANDARD. IT SHALL NOT BE REPRODUCED OR CIRCULATED OR QUOTED, IN WHOLE OR IN PART, OUTSIDE OF ASTM COMMITTEE ACTIVITIES EXCEPT WITH THE APPROVAL OF THE CHAIRPERSON OF THE COMMITTEE HAVING JURISDICTION AND THE PRESIDENT AND PRESIDENT OF THE SOCIETY. (© ASTM)

1.0 Scope

- 1.1 These test methods cover general guidelines for the assessment of the effectiveness of products and materials intended to replace, restore or regenerate the function or properties of skin. Such products may be composed of one or more of the following: natural or synthetic biomaterial, cells, or biologically active molecules.
- 1.2 Test methods include a range of species and sizes of animals.
- 1.3 This assessment document does not contain methods describing preparation and formation of biomaterials into devices. It does not describe methods for the addition of cells or bioactive molecules. ASTM standards for these methods are available and they are listed in section 2 of this document.
- 1.4 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices, and to determine the applicability of regulatory limitations prior to use.*

2.0 Reference Documents

3.0 Terminology (Ref F04.43.05)

- 3.1 Primary Components
- 3.2 Site of Action
- 3.3 Therapeutic Target
- 3.4 Therapeutic Effect
- 3.5 Primary Modes of Action
- 3.6 Duration of Therapy
- 3.7 Life of TEMP
- 3.8 Other

4.0 Materials Characterization

4.1 Cells / tissue (ref F04.45)

Cells/ tissue will be evaluated on presence of transmissible components before processing.

<u>Cells or tissue</u>	<u>Allogeneic</u> <ul style="list-style-type: none"><input type="checkbox"/> <u>Screening of patient medical records for risk factors or clinical evidence of communicable disease</u><input type="checkbox"/> <u>Donor testing to reduce transmission of relevant communicable diseases at minimum: HIV type 1 and 2, Hepatitis B and C, Treponema pallidum, Human T-Lymphotropic virus type 1 and 2 and cytomegalo virus in leukocyte rich cells or tissue</u>
	<u>Autologous</u> <ul style="list-style-type: none"><input type="checkbox"/> <u>Screening or testing is recommended in current regulation proposals, however not required</u>
	<u>Xenogeneic</u> <ul style="list-style-type: none"><input type="checkbox"/> <u>Framework of animal source screening to minimize potential cross-species transmission of known and zoonotic agents. Testing depends on donor species and geographical region</u>

Cells will have to be characterized on availability of proper cell population, which should be formulated in design input. Following testing can be considered, cell identity (PCR), cell morphology, cell purity, cell potency (?)

Cell properties during process before seeding cells to the scaffold/ matrix or and at final product release stage will be evaluated during design review. Such properties could include, but are not limited to cell viability, cell morphology, cell yield.

4.2 Biomolecules (in association with F04.44)

Biomolecules may be added to the skin TEMP for the purpose of modulating the host tissue and organ response to an injury or defect in the integument. Biomolecules are, for example, growth factors, cytokines, synthetic peptides or genetic molecules.

Biomolecules properties will be evaluated and identified during design review. The inclusion of parameters will be determined by the product's design. Such properties could include but are not limited to purity, in vitro potency, and in vivo activity utilizing a suitable pre-clinical model.

4.3 Biomaterials (in association with F04.43)

Biomaterials are the scaffold or matrix that comprises the bulk of the skin TEMP. They are either natural or synthetic biomaterials. Biomaterial properties will be evaluated and identified during design review. The inclusion of parameters will be determined by the requirement of the product's design. Such properties could include but are not limited to strength and other mechanical properties, chemical composition, purity, microstructure (porosity), and overall appearance

4.4 Sterilization and aseptic processing methods

Level of sterility may have to be defined in the design input. Sterility tests should demonstrate(validation) that culture methods and processing steps do not introduce any viral or other pathogens. Sterility could be evaluated at formal product release stage. Reduced version of USPXXIII, which is validated could be performed in order release products within suitable timeframe

5.0 Pre-clinical Safety

Microbiological See 4.4

Biocompatibility test will be evaluated in order to define safety of the end product. Test should be conducted according to ISO 10993-1 matrix. For most end products it will not be feasible to test this in various biocompatibility animal models (ISO 10993) since most of the test are conducted with cells of a specific animal specimen. Where possible animal test as mentioned mentioned in ISO 10993 will be conducted unless justification is provided.

6.0 Pre-clinical Efficacy

Animal models in the evaluation of skin substitutes and tissue regeneration

The wound model in the athymic nude mice and rat.
Due to a genetic defect the spleen has not developed in these animals. As a consequence the specific immune response is impaired since T cell maturation after birth is not possible. The main advantage of these animal models is that skin substitutes populated with human cells can be evaluated without evoking immune-rejection reactions. These wound models often have been used to study epidermal regeneration¹⁻³, basement membrane formation⁴, angiogenesis⁵, wound contraction^{6,7}, biodegradation⁸ and

optimisation of living skin equivalents⁹⁻¹¹. This wound model is less suited to study scar formation since the dermal architecture is not comparable to that of human skin¹². In the evaluation of treatments of hypertrophic scars, the athymic nude mice and rat are also good in vivo model¹³. Implantation of in humans removed hypertrophic scar tissue allows the evaluation of topical and systemic treatments.

The diabetic mice and rat wound model

The diabetic mouse is most suited model to study impaired wound healing caused by diabetes. The model has been used to evaluate treatments, which stimulate wound healing^{14,15}. However with the extrapolation of results to clinical situation care should be taken. The diabetic mice resembles most to Type I diabetes in humans, and most patients with a diabetic ulcer have Type II diabetes.

Wound healing models in mice, rats, guinea pigs and rabbits

The mice, rats, guinea pigs and rabbits wound models are suitable to be used for studies investigating biodegradation of and inflammatory responses against materials developed as scaffolds for tissue engineering. Furthermore, these models do allow to some extent the evaluation of tissue regeneration for which intra-individual comparison should be the preferred method use. With these models one has to take in consideration that rodents and rabbits have different skin architecture with different mechanical properties when compared to human skin¹² and it is likely that scar formation is also different when compared to humans. The rabbit ear wound model is a good wound model to study healing in relation to angiogenesis and mimics best impaired wound healing associated with blood flow alterations¹⁶.

The wound models in pigs

The pig is the most relevant wound model to study wound healing and dermal tissue regeneration, wound contraction and scar formation¹⁷⁻²⁴, because its skin resembles human skin most, morphologically as well as functionally^{12,25}. In addition because of the large skin area the pig allows good intra-individual comparison. In pigs, however, hypertrophic scarring like in humans does not seem to occur.

7.0 Clinical Studies (in association with F04.48)

Appropriate clinical study, either trials to determine safety and efficacy or clinical evaluations will be used to assess the utility of skin TEMP. Such studies will comply with all regional standards of patient protection and

privacy. Each study will follow a prospectively designed plan and can include but is not limited to these descriptions: study article, control material, patient inclusion and exclusion criteria, clinical endpoints, primary and secondary, statistical plan and adverse event reporting procedures.

8.0 Long Term follow-up – clinical results

Skin wound healing and the associated reparative processes are widely recognized to require time periods that routinely exceed study duration periods. The design of the skin TEMP may require long-term patient follow-up to determine if these properties have been achieved. An example is the achievement of improved appearance of the regenerated skin: a cosmetic advantage.

Bibliography

1. Krejci NC, Cuono CB, Langdon RC, McGuire J. In vitro reconstitution of skin: fibroblasts facilitate keratinocyte growth and differentiation on acellular reticular dermis. J Invest Dermatol 1991;97:843-8.
2. Harriger MD, Warden GD, Greenhalgh DG, Kagan RJ, Boyce ST. Pigmentation and microanatomy of skin regenerated from composite grafts of cultured cells and biopolymers applied to full-thickness burn wounds. Transplantation 1995;59:702-7.
3. Medalie DA, Eming SA, Collins ME, Tompkins RG, Yarmush ML, Morgan JR. Differences in dermal analogs influence subsequent pigmentation, epidermal differentiation, basement membrane, and rete ridge formation of transplanted composite skin grafts. Transplantation 1997;64:454-65.
4. Cooper ML, Hansbrough JF, Boyce ST, Foreman TJ. Rapid Formation of Anchoring Fibrils and Basement Membrane after Placement of Dermal-Epidermal Composite Cultured Skin Substitutes on Full-Thickness Wounds. Surg Forum 1991;584-6.
5. Eming SA, Medalie DA, Tompkins RG, Yarmush ML, Morgan JR. Genetically modified human keratinocytes overexpressing PDGF-A enhance the performance of a composite skin graft. Human Gene Therapy 1998;9:529-39.
6. Boyce ST, Foreman TJ, English KB, Stayner N, Cooper ML, Sakabu S, et al. Skin wound closure in athymic mice with cultured human cells, biopolymers, and growth factors. Surgery 1991;110:866-76.
7. Boyce ST, Supp AP, Harriger MD, Greenhalgh DG, Warden GD. Topical nutrients promote engraftment and inhibit wound contraction of cultured skin

substitutes in athymic mice. Journal of Investigative Dermatology 1995;104:345-9.

8. Harriger MD, Supp AP, Warden GD, Boyce ST. Glutaraldehyde crosslinking of collagen substrates inhibits degradation in skin substitutes grafted to athymic mice. Journal of Biomedical Materials Research 1997;35:137-45.

9. Wilkins LM, Watson SR, Prosky SJ, Meunier SF, Parenteau NL. Development of a bilayered living skin construct for clinical applications. Biotechnology & Bioengineering 1994;43:(pp 747-756).

10. Hansbrough JF, Morgan JL, Greenleaf GE, Bartel RL. Composite grafts of human keratinocytes grown on a polyglactin mesh-cultured fibroblast dermal substitute function as a bilayer skin replacement in full-thickness wounds on athymic mice. J Burn Care Rehabil 1993;14:485-94.

11. Cooper ML, Hansbrough JF, Spielvogel RL, Cohen R, Bartel RL, Naughton G. In vivo optimization of a living dermal substitute employing cultured human fibroblasts on a biodegradable polyglycolic acid or polyglactin mesh. Biomaterials 1991;12:243-8.

12. Meyer W, Schwarz R, Neurand K. The skin of domestic mammals as a model for the human skin, with special reference to the domestic pig. Curr Probl Dermatol 1978;7:39-52.

13. Kischer CW, Pindur J, Shetlar MR, Shetlar CL. Implants of hypertrophic scars and keloids into the nude (athymic) mouse: viability and morphology. J Trauma-Inj Inf & Crit Care 1989;29:672-7.

14. Matuszewska B, Keogan M, Fischer DM, Soper KA, Hoe CM, Huber AC, et al. Acidic fibroblast growth factor evaluation of topical formulations in a diabetic mouse wound healing model. Pharm Res 1994;11:65-71.

15. Broadley KN, Aquino AM, Hicks B, Ditesheim JA, McGee GS, Demetriou AA, et al. The diabetic rat as an impaired wound healing model: stimulatory effects of transforming growth factor-beta and basic fibroblast growth factor. Biotechnol Ther 1990;1:55-68.

16. Zhao LL, Davidson JD, Wee SC, Roth SI, Mustoe TA. Effect of hyperbaric oxygen and growth factors on rabbit ear ischemic ulcers. Arch Surg 1994;129:1043-9.

17. Dyson M, Young S, Pendle CL, Webster DF, Lang SM. Comparison of the effects of moist and dry conditions on dermal repair. J Invest Dermatol 1988;91:434-9.

18. de Vries HJC, Middelkoop E, van Heemstra-Hoen M, Wildevuur CHR, Westerhof W. Stromal cells from subcutaneous adipose tissue seeded in a native collagen/elastin dermal substitute reduce wound contraction in full thickness skin defects. Lab Invest 1995;73:532-40.

19. Lamme EN, de Vries HJC, van Veen H, Gabbiani G, Westerhof W, Middelkoop E. Extracellular matrix characterization during healing of full-thickness wounds treated with a collagen/elastin dermal substitute shows improved skin regeneration in pigs. J Histochem Cytochem 1996;44:1311-22.

20. Kangesu T, Navsaria HA, Manek S, Fryer PR, Leigh IM, Green CJ. Keratodermal grafts: the importance of dermis for the in vivo growth of cultured keratinocytes. Br J Plast Surg 1993;46:401-9.

21. Carver N, Navsaria HA, Green CJ, Leigh IM. Acute rejection of cultured keratinocyte allografts in nonimmunosuppressed pigs. Transplantation 1991;52:918-21.

22. Butler CE, Orgill DP, Yannas IV, Compton CC. Effect of keratinocyte seeding of collagen-glycosaminoglycan membranes on the regeneration of skin in a porcine model. Plastic & Reconstructive Surgery 1998;101:1572-9.

23. Reagan BJ, Madden MR, Huo J, Mathwich M, Staiano-Coico L. Analysis of cellular and decellular allogeneic dermal grafts for the treatment of full-thickness wounds in a porcine model. Journal of Trauma 1997;43:458-66.

24. Hinrichsen N, Birk-Sorensen L, Gottrup F, Hjortdal V. Wound contraction in an experimental porcine model. Sca J Plast Reconstr Surg & Hand Surg 1998;32:243-8.

25. Winter GD. Oxygen and epidermal wound healing. Adv Exp Med Biol 1977;94:673-8.

FedEx USA Airbill FedEx Tracking Number 821168800273

SP013
Form I.D. No. 0215 Recipient's Copy

From This portion can be removed for Recipient's records.
Date 8-25-00 FedEx Tracking Number 821168800273

Sender's Name Browning Phone 312 642-9260

Company AMERICAN BURN ASSOCIATION

Address 625 N MICHIGAN AVE STE 1530 Dept./Floor/Suite/Room

City CHICAGO State IL ZIP 60611

2 Your Internal Billing Reference

3 To Recipient's Name Dockets Management Branch Phone

Company Food & Drug Administration

Address 5630 Fishers Lane Dept./Floor/Suite/Room

We cannot deliver to P.O. boxes or P.O. ZIP codes.
Room 1061

To "HOLD" at FedEx location, print FedEx address here.
City Rockville State MD ZIP 20850



0143670962

4a Express Package Service

FedEx Priority Overnight Next business morning
 FedEx Standard Overnight Next business afternoon
 FedEx First Overnight Earliest next business morning delivery to select locations.
 FedEx 2Day* Second business day
 FedEx Express Saver* Third business day
Packages up to 150 lbs. Delivery commitment may be later in some areas.
Packages over 150 lbs. Delivery commitment may be later in some areas.
* FedEx Letter Rate not available. Minimum charge: One-pound rate.

4b Express Freight Service

FedEx 1Day Freight* Next business day
 FedEx 2Day Freight Second business day
 FedEx 3Day Freight Third business day
* Call for Confirmation.
* Declared value limit \$500.

5 Packaging

FedEx Letter* FedEx Pak* Other Pkg. Includes FedEx Box, FedEx Tube, and customer pkg.

6 Special Handling

Saturday Delivery Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes.
 Sunday Delivery Available for FedEx Priority Overnight to select ZIP codes.
 HOLD Weekday at FedEx Location Not available with FedEx First Overnight.
 HOLD Saturday at FedEx Location Available for FedEx Priority Overnight and FedEx 2Day to select locations.

Does this shipment contain dangerous goods? (The box must be checked.)
 No Yes As per attached Shipper's Declaration Yes Shipper's Declaration not required
 Dry Ice Dry Ice, 3, UN 1845 x kg
Dangerous Goods cannot be shipped in FedEx packaging. Cargo Aircraft Only

7 Payment Bill to:

Enter FedEx Acct. No. or Credit Card No. below. Obtain Recip. Acct. No.
 Sender Acct. No. in Section 1 will be billed. Recipient Third Party Credit Card Cash/Check

Total Packages Total Weight Total Charges
Credit Card Auth.

8 Release Signature Sign to authorize delivery without obtaining signature.

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.
Questions? Call 1-800-Go-FedEx (800-463-3339)
Visit our Web site at www.fedex.com
Rev. Date 1/19/99-P&L 4/99

359

The World Or
BURN

DELIVERY OVERNIGHT MON
PRIORITY OVERNIGHT MON

FORM 0215
Trk# 8211 6880 0273

20852 -MD-US

IAD
XAGAIRA

