

FDA Part 15 Public Hearing  
Combination Products Containing Living Cells  
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02N-0169

Slide 1:

Good afternoon. I am Steven Boyce. I am trained as a cell biologist, and I currently hold positions as Associate Professor in the Department of Surgery at the University of Cincinnati, as Senior Investigator and Director of the Department of Tissue Engineering at the Shriners Burns Hospital in Cincinnati, as Founder and President of Cutanogen Corporation, a biotechnology development company, and as an *ad hoc* reviewer for the Advisory Panel to the General and Plastic Surgery Devices Branch of CDRH. For more than 20 years, I have conducted preclinical and clinical studies on a combination of cultured skin cells and biopolymers for prospective treatment of skin wounds. Clinical studies have been conducted under Investigational Device Exemptions for more than 10 years. These studies and those of numerous other academic and corporate laboratories have responded to extensive medical needs for management and healing of skin wounds

My remarks are my professional opinions and my understanding of this field based on my training and experience, but are not represented to be accurate interpretations of FDA policy, of regulatory jurisdictions of existing products, or to be all inclusive or exclusive.

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The extensive medical needs for wound closure may be divided into three main categories:

- 1) Acute/emergent as occur in burns over large total body surface areas (TBSA), or toxic epidermal necrosis,
- 2) Acute/elective as occur in reconstructive surgery, and,
- 3) Chronic/elective, as occur in skin ulcers of multiple etiologies.

and two subcategories:

- a) Full-thickness which usually require grafting with split-thickness skin graft to accomplish wound closure, and
- b) Partial-thickness which usually will close spontaneously if kept clean and protected with conventional dressings.

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Medical risks associated with these categories of wounds are proportionate with the magnitude of the injury and with the consequent compromise of the protective functions of skin. If medical risks were scaled from high to low, factors contributing to high risks would include skin wounds with:

- 1) emergent etiology,
- 2) great magnitude (>50% TBSA),
- 3) full-thickness depth, and
- 4) associated injury or disease.

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To emphasize this point, (insert plot) data from the 2002 Report of the National Burn Repository show mortality from burns increases from less than 1% of patients with burns of less than 10% TBSA, to about 66.9% of patients with 80-90%TBSA burns. Conversely, the predominant majority of patients with chronic wounds may die with a chronic wound, but will not die from a chronic wound.

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In response to this variety of medical needs and relative risks, multiple approaches have been designed, tested and implemented to restore the structure and function of healthy skin. Because healthy skin consists of two main anatomic components, epidermis and dermis, replacements for each of these components have been designed and tested. Although healthy skin provides a multitude of structures and functions for the human body, the essential properties for stable wound closure are restoration of the “three B’s”: epidermal barrier, basement membrane, and blood supply in stable connective tissue.

Healthy epidermis consists almost entirely of cells (keratinocytes, melanocytes, immunocytes) with minimal extracellular matrix, whereas natural dermis is predominantly matrix with low densities of cells (fibroblasts, endothelial cells, nerve, immunocytes). Consequently, common approaches to replacement of epidermis have involved cells without matrix, and delivery of a dermal substitute has included acellular polymers from either biologic (e.g., collagen) or synthetic (e.g. poly-lactic/poly-glycolic acids) sources with or without cells. In all cases, the polymers are a degradable type which have been regulated historically by CDRH. Furthermore, if cells are contained in the therapy, they may be from autologous or allogeneic sources with autologous cells able to persist indefinitely after engraftment, and allogeneic cells being lost from the treatment site by immune degradation.

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This table summarizes the Cincinnati skin substitute and some products approved for treatment of skin wounds that are acellular or cellular, and combinations of polymers and cells.

(The table is not represented to be all-inclusive or exclusive.)

<i>Component</i>	<i>Acellular</i>	<i>Allogeneic</i>	<i>Autologous</i>
Both	Integra™	Apligraf™, Orcel™	Cincinnati Skin Substitute
"Epidermis"			Epicel™
"Dermis"	Alloderm™	DermaGraft™ (not live cells)	

Depending on the magnitude and depth of the skin wound, either allogeneic or autologous cells may result in permanent closure of an open wound. For example, combination materials containing allogeneic cells (e.g., Apligraf) have been demonstrated to promote closure of chronic wounds of limited size, but allogeneic cells will not close an extensive, full-thickness burn. At present, only autologous cells can provide direct structural and functional restoration by transplantation to the diseased site, whereas allogeneic cells act indirectly to deliver cytokines and extracellular matrix that stimulate healing by autologous cells of the recipient. In either case where living, metabolically active cells are applied, the mechanisms of healing are clearly biologic. The biologic contribution to the mode of action of a combination material can be easily quantified in controlled preclinical studies that compare the combination material to the acellular vehicle. Acellular materials alone have been demonstrated to promote dermal repair by recruitment and ingrowth of surrounding tissue, or by combination with a split-thickness skin autograft. However, the composition of the material may be derived from processing of a natural tissue (i.e., AlloDerm™), or by extraction of

purified compounds that are fabricated with specific structural and biochemical characteristics that can be distinguished from natural tissue (i.e., Integra™). The former is considered a processed tissue, while the latter is considered a medical device.

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The Cincinnati model of cultured skin substitute has been used successfully to treat and close burns of greater than 50% TBSA in dozens of patients, and has demonstrated clinically significant reduction of donor site requirements to complete wound closure. At the time of surgery, this material consists almost entirely of cells (lower right), and acts by delivering to the wound functional epidermal barrier, basement membrane and angiogenic factors that stimulate vascularization and biological engraftment of the transplanted cells within 5 days after surgery.

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Culture of cells with a polymer in permissive media also allows development of basement membrane in vitro as shown in these micrographs. Immuno-staining for basement membrane antigens, collagen VII and laminin 5, demonstrate high fidelity of the natural bond between the epidermis and dermis of natural skin on the left, and the skin substitute on the right.

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The clinical relevance of basement membrane formation is dramatized by a case of a child with an 80% burn who was treated with Epicel at another hospital until he was transferred to the Cincinnati Shriners Hospital for definitive care. The upper left panel shows the effective treatment of wounds on the leg with the Cincinnati skin substitute, with no blistering or secondary loss of the healed skin. In contrast, sites treated with Epicel blistered extensively as shown in the lower left

panel, and resulted in extensive open wounds as shown on the right. This patient is currently planned for complete resurfacing of the Epicel sites with the Cincinnati skin substitute. This case emphasizes importantly the greater efficacy of a combination of skin cells with a polymeric delivery vehicle compared to epidermal cells alone. Yet the combination material in Cincinnati is considered a Class III (Significant Risk) device under regulation of CDRH with mandatory multi-center studies, and Epicel (to the best of my knowledge) is considered a Humanitarian Use Device with no requirement for performance or review by FDA of multi-center studies.

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The clinical efficacy of the Cincinnati skin substitute results almost entirely from cellular processes that, at present, cannot be duplicated by acellular chemical reactions performed in the laboratory. The effectiveness of this material reduces greatly the life-threatening risks of extensive, full-thickness burns, by restoration of the protective functions of healthy skin as shown in this survivor of a greater than 90% TBSA burn.

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Comparative clinical studies of this skin substitute to split-thickness skin autograft have demonstrated rates of engraftment that are not different statistically, and a definitive benefit of reduction of donor skin has been demonstrated by expansion ratios of about 65 times the area of donor skin versus a maximum of 4 for autograft.

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Optimal results for wound closure and skin pliability have obtained by combination of this skin substitute with the dermal substitute Integra, most probably because the Integra generates a uniform base of vascularized connective tissue that promotes engraftment, and reduces formation

of granulation tissue. If this graft base is closed with functional epidermal barrier, the inflammatory process that generates scar is inhibited and the resulting skin is smooth, soft and strong.

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The same benefits have been demonstrated in a limited number of cases of burn scar after pretreatment with cadaver allograft, and

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For treatment of giant congenital nevus which also may involve large TBSAs, and require full-thickness excision followed by closure with autologous skin grafts. This patient was treated with split-thickness skin autograft, and was subsequently treated with the Cincinnati skin substitute to reduce morbidity from harvesting of donor skin.

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Engraftment was rapid and almost complete at Post-operative day 15 with no regrafting, and an outcome virtually identical to autograft at one year.

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This material may also be prepared with allogeneic cells, and has been used successfully to treat chronic wounds.

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Overall experience and data generated with the Cincinnati skin substitute have shown that it: conserves or eliminates donor skin for wound closure; has virtually no blistering and minimal regrafting; and produces minimal scar. However, the past and current regulation of this

combination of cells and matrix is considered a Class III (Significant Risk) device under the jurisdiction of CDRH.

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The collagen-based substrate used in this material is virtually identical in composition and performance to several kinds of implantable collagen materials that are known to be very safe and efficacious, yet the substrate's use in this combination material cannot currently be approved by a 510k mechanism. If the substrate were not combined with cells, most probably it would be a device of low risk due to the extensive experience and known safety and efficacy of similar materials. However, because there is no predicate, it is considered a Class III (Significant Risk) device which requires performance of multi-center clinical studies before marketing approval.

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In addition to the relative risks of disease etiology described above, risks may result from the sources of starting materials or the processing of the proposed material. For autologous tissues the FDA Guidance for "Minimally-manipulated autologous tissue for Structural Repair (MAS)" requires assurances of safety by facilities registration and processing controls, but multi-center clinical studies are not mandatory. However, FDA's MAS Guidance may not make adequate considerations of the risks associated with loss of efficacy from isolation, proliferation and implantation of cells without a matrix. Combination materials for skin repair with autologous cells may provide greater fidelity to native skin by providing both epidermal and dermal components, and by regenerating epidermal barrier, basement membrane and stimulation of vascularization. The development of functional phenotypes increases skin repair and decreases patient risk, but FDA has historically considered combination materials to have greater risk than grafts of single cell types. Under the MAS Guidance, clinical comparison of isolated cells to the prevailing standard of

care may not be required. In my opinion and experience, the greater anatomic and physiologic fidelity to natural skin of combination materials (i.e., Cincinnati skin substitute) increases the benefit-to-risk ratio to patients more than single cell types without matrix (i.e., Epicel). And as stated above, if the composition of a device matrix is similar to an existing, approved material, then the matrix component should be reviewed under a 510k mechanism because its composition and performance are predictable and of limited risk.

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From this perspective, combination materials made with autologous cells should be able to follow the general path to market that is permitted by the MAS Guidance which is under the jurisdiction of CBER with a parallel 510k review of the matrix by CDRH. Regulatory requirements that extend farther than this result in unnecessary delays to entry of new therapies into clinical care, without identification of additional risk, except the lack of a precedent in clinical practice. These delays can result in mortality and morbidity to patients.

This flow diagram summarizes the suggested jurisdictions of CBER and CDRH for combination products with autologous cells.

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If polymers or cells are derived from allogeneic sources, the standards established by the American Association of Tissue Banks have provided for conditions of tissue harvesting processing and tracking, optimal assurances of safety from disease transmission (microbial or viral), and facilities accreditation. These standards together with FDA's requirements for determination of donor suitability, facilities registration and inspection, and the developing Good Tissue Practices (GTPs) provide a very positive benefit-to-risk ratio to recipients of transplanted tissues from allogeneic sources. Historically, these requirements have been sufficient to allow release of tissue for transplantation without the need for pre-market approval or multi-center study. However, if

additional processing of tissues occurs to isolate or derive an acellular or cellular component from allogeneic tissue, then the additional processes may be subject to review to assure that biological, chemical or physical risks are not introduced from processing. Furthermore, those processes may denature or degrade the structure and function of the original tissue, to an extent that compromises its efficacy. Demonstration that processing of tissues does not introduce risks, or degrade efficacy may be advisable to assure that the processed material provides the safety and efficacy of the natural tissue. These assurances can be provided by direct comparisons between the processed tissue and the natural tissue in preclinical studies to determine whether or not efficacy is maintained.

In comparison, current FDA standards for materials containing living cells combined with a matrix also require assurances of safety. Because most of the combination materials for skin repair have no predicate and have been considered devices, each has been classified by default as a Class III (Significant Risk) device under CDRH. Although the assumption that combination materials are high risk provides a conservative position that may provide maximum protection to patients, without determination that a risk from the therapy actually exists, this conservative position may reduce availability of the therapy to patients whom are at greater risk from their disease condition (i.e., extensive burns). The Class III device designation of CDRH requires demonstration of clinical efficacy in multi-center (pivotal) studies to gain marketing approval, and cGMP manufacturing. However, because the primary mode of action is cellular, the assignment of jurisdiction to CDRH provides more limited consideration of the biological origins and actions of the cellular components, and may require more stringent conditions for manufacturing under cGMP than for tissue processing under GTP standards. Assuming that all cellular products are handled in Class 100 biological safety cabinets, incubated in Hepa-filtered incubators, and handled by trained staff wearing protective clothing, more important to the material safety than the manufacturing environment is the composition and origin of the reagents through which the cells pass during

processing.

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This flow diagram summarizes the suggested jurisdictions of CBER and CDRH for combination products with allogeneic cells.

(Slide 23) In summary:

1) Combination materials of cells and polymeric matrix usually consist of mostly cells, and act predominantly by cellular mechanisms, either direct as with autologous cells, or indirect as with allogeneic cells. The contribution of the cellular components can be determined in preclinical studies that compares the combination material to the matrix alone.

2) Risks associated with combination products made with autologous cells should be considered no greater than minimally manipulated autologous tissue. In fact, risks are less because biologic fidelity to the natural tissue is usually greater.

3) For combination products with allogeneic cells, standards of the American Association of Tissue Banks and the developing Good Tissue Practices of the FDA provide adequate assurances of tissue safety to patients to maintain a very favorable benefit-to-risk ratio for most disease conditions.

(Slide 24) In conclusion:

1) If the primary mode of action of a combination of cells with matrix is cellular, then the jurisdiction should be under CBER, not CDRH. If the primary mode of action is the matrix, then CDRH should have jurisdiction. The acellular matrix component should be reviewed by CDRH.

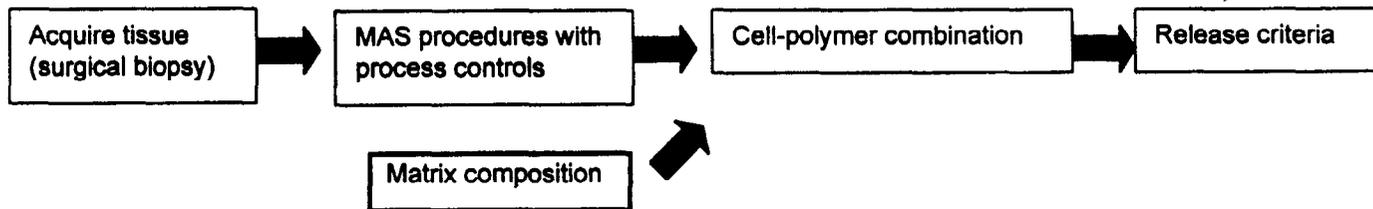
2) If the jurisdiction for combination products is under CBER, then pre-market approval should require safety assurances and facilities requirements as in tissue banking (registration, GTPs), but not include mandatory multi-center trials to demonstrate efficacy in comparison to a prevailing standard of care. If autologous cells are used in the material, the MAS Guidance should be followed for the cellular component. If allogeneic cells are used, then tissue banking practices should become the reference standard. Process controls and release criteria that are specific to the material should be required to provide assurances of safety. Any additional procedures or reagents not typically used in tissue banking (animal cells or by-products) should be reviewed for consideration of safety before marketing approval, and most frequently these will be biologic.

3) Most combination products should not require multi-center studies unless the sponsor is seeking specific product claims.

Below are flow diagrams in which general practices and FDA jurisdictions are suggested for combination materials with a primary mode of action that is from living cells:

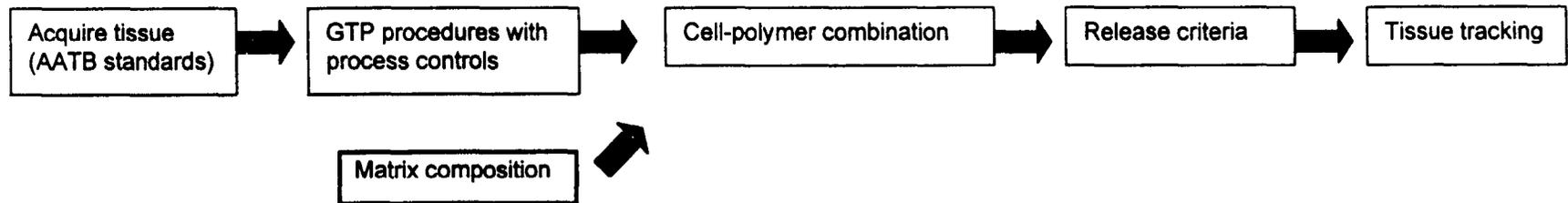
For combination products with *autologous cells*:

Acquire, process and release like MAS under CBER. Matrix approval by CDRH. Multi-center studies not mandatory.



For combination products with *allogeneic cells*:

Acquire, process, release and tracking like tissue banking (AATB stds for microbial and viral testing, GTPs) under CBER. Matrix approval by CDRH. Multi-center studies not mandatory.



Legend:

CBER regulation

CDRH regulation