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Combination Products Containing Live Cellular Components

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APLIGRAF®

- A living, bi-layered, skin substitute consisting of
 - an epidermal layer formed by human keratinocytes with a well-differentiated stratum corneum
 - a dermal layer composed of human fibroblasts in a bovine Type I collagen lattice
 - matrix proteins and cytokines found in human skin
 - does not contain Langerhans cells, melanocytes, macrophages, lymphocytes, blood vessels or hair follicles

Apligraf® is sold in the United States by Novartis Pharmaceuticals Corporation

APLIGRAF



APLIGRAF REGULATORY PATHWAY

- 1985 - Organogenesis established to commercialize lead product Apligraf ●
- 1986 - FDA designated Apligraf as a device
- 1987 - IDE submitted
- 1995 - PMA submitted
- 1998 - PMA approved for treatment of venous leg ulcers ●
- 2000 - PMA supplement approved for treatment of diabetic foot ulcers

APLIGRAF APPROVED INDICATIONS

- Apligraf is indicated for use with standard therapeutic compression for the treatment of non-infected partial and full-thickness skin ulcers due to venous insufficiency of greater than 1 month duration and which have not adequately responded to conventional ulcer therapy ●
- Apligraf is also indicated for use with standard diabetic foot ulcer care for the treatment of full-thickness neuropathic diabetic foot ulcers of greater than three weeks duration which have not adequately responded to conventional ulcer therapy and which extend through the dermis but without tendon, muscle, capsule or bone exposure ●

MANUFACTURING CONTROLS

- Maternal donor screening and testing
- Master Cell Bank and Working Cell Bank testing ●
- Qualification of reagents including animal-derived materials
- Aseptic processing
- Compliance with Quality System Regulation
- In-process testing ●
- Final release specifications e.g. sterility and histology

APLIGRAF SAFETY TESTING

Maternal Blood

HIV-1 (Ab)
HIV-2 (Ab)
HIV-p24 (Ag)
HTLV-1 (Ab)
HTLV-2 (Ab)
Hepatitis A (Ab)
Hepatitis B surface (Ab, Ag)
Hepatitis B core (Ab)
Hepatitis B (Ab)
Hepatitis C (Ab)
Cytomegalovirus (Ab)
Epstein-Barr virus (Ab)
Syphilis (RPR)

Cell Banks

HIV-1 (PCR)
HIV-2 (PCR)
HIV-p24 (Ag)
HTLV-1 (PCR)
HTLV-2 (PCR)
Hepatitis A (PCR)
Hepatitis B surface (Ag)
Hepatitis C (PCR)
Cytomegalovirus (culture)
Epstein-Barr virus (PCR)
Bacteria, fungi, yeast (culture)
Mycoplasma (culture)
In vitro virus (culture)
In vivo virus (culture)
Karyology (microscopy)
Isoenzymes (analytical)
Virus by EM (microscopy)
Retrovirus by RT (microscopy)
Herpesvirus 6 (culture)
Herpesvirus 7 (PCR)
Tumorigenicity (culture)
Human Papilloma (PCR)

CLINICAL TRIALS

- Randomized, controlled clinical trials comparing Apligraf to the standard of care to establish safety and efficacy
 - Definition of primary endpoint
 - Procedural-based study
 - Active control groups
 - Unmasked study design
 - Use of photographs
 - Adverse event reporting
 - Immunology
- Comparators for wound healing studies are devices
- Use of appropriate statistical techniques to account for factors influencing wound healing
 - Outcome survival analyses
 - Multi-variate regression models

PUBLIC HEALTH CONSIDERATIONS

- No public safety concern exists to support a jurisdictional change
- Apligraf has shown a strong safety profile
 - Over 50,000 patients have been treated with Apligraf
 - Incidence of Medical Device Reports less than 0.01%
 - Adverse events are localized to wounds - infection, cellulitis, edema, erythema, inflammation
 - Adverse event reporting comparable to standard care
- Adequately addressed by FDA policies and practices
 - Guidance Document – “Chronic Cutaneous Ulcer and Burn Wounds - Developing Products for Treatment”
 - 21 CFR 1271: Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps)

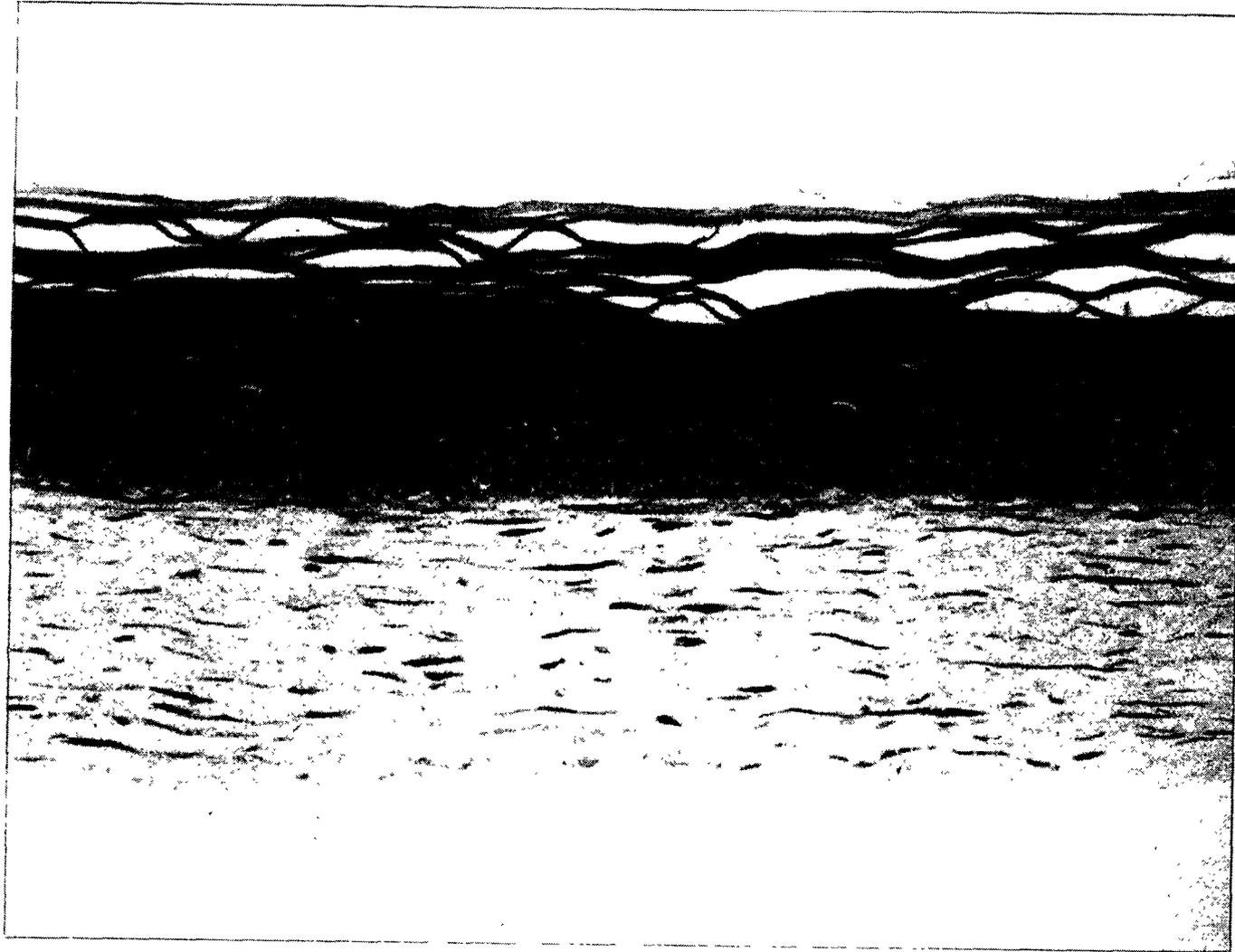
WOUND HEALING

- Complicated process
 - Acute wound healing involves complex cascade of overlapping events at wound site
 - In chronic wounds there is a failure to progress through a normal, orderly, and timely sequence of wound repair
 - Not caused by a single event

APLIGRAF AS A SINGLE ENTITY

- Apligraf is a single entity by its structure and function
 - Structural attributes
 - Cellular components are integrated into the acellular matrix resulting in a cellular wound dressing with specified dimensions
 - Apligraf is released based on histological criteria of the structure
 - Functional attributes
 - Applied as one unit to a local wound site
 - Apligraf acts as a wound covering and performs the barrier function of skin
 - Apligraf produces cytokines found in normal human skin
 - The components come together to work as an integrated unit

APLIGRAF HISTOLOGY



LOCALIZED EFFECT OF APLIGRAF

- Systemic adverse events have not been attributed to Apligraf
- Apligraf's physical properties provide immediate wound coverage and barrier function
- Localized effect on wound healing
 - Does not affect healing of non-contiguous ulcers
- No evidence of absorption or metabolism of Apligraf
- Apligraf's therapeutic effect is localized

MODE OF ACTION

- Cells make final structure of Apligraf possible, but cannot be separated either physically or functionally from the matrix ●
- Unable to determine quantitative contributions of components of Apligraf
- Unable to determine a single mode or a primary mode of action of Apligraf ●

FACTORS FOR JURISDICTION ASSIGNMENT

- Since it is not possible to determine the primary mode of action, the following factors should be considered
 - Intended use – wound healing
 - Overall structural and functional properties
 - Safety testing of components
 - Manufacturing controls
 - Randomized, controlled clinical trials
 - Post-marketing adverse event reporting
- The current regulatory paradigm in place under CDRH is effective
- CDRH placement does not preclude inter-center collaborative review

CDRH REGULATION OF WOUND HEALING PRODUCTS

- Jurisdiction established by the Medical Device Amendments of 1976
- Developed expertise and knowledge in the issues unique to wound healing
- FDA guidance documents address issues regarding wound healing products with living cells
- Patients and health care providers have benefited as additional wound treatment options have become available
- Implemented and consistently applied regulatory controls to ensure only safe and effective products introduced to market

CONCLUSION

Maintaining the current regulatory structure with wound healing products assigned to the jurisdiction of CDRH will assure adequate review of new technologies, continue to protect the public health and advance the field of wound care.