

41 41

Combination Products Containing Live Cellular Components

Date and Location:

Date: June 24, 2002

Time: 9:00 - 5:00 p.m.

Location:

The Double Tree Hotel

1750 Rockville Pike

Plaza II & III

Rockville, MD 20852

7:00
7:15
7:30
7:45
8:00
8:15
8:30
8:45
9:00
9:15
9:30
9:45
10:00
10:15
10:30
10:45
11:00
11:15
11:30
11:45
12:00
12:15
12:30
12:45
1:00
1:15
1:30
1:45
2:00
2:15
2:30
2:45
3:00
3:15
3:30
3:45
4:00
4:15
4:30
4:45
5:00

Presentation by Ortec International, Inc:

Good [morning/afternoon]. My name is Costa Papastephanou, and I am the President of Ortec International, Inc. Ortec is a tissue-engineering company involved in the commercialization of a proprietary and patented technology to stimulate the repair and regeneration of human tissue. Ortec's current focus is in the application of its OrCel™ Bilayered Cellular Matrix to heal chronic and acute wounds. OrCel is composed of a collagen matrix seeded with allogeneic epidermal and dermal cells. These cells secrete growth factors and cytokines normally found in acute human wounds and are believed to create an environment that may have a beneficial role in promoting tissue repair. In addition to having received FDA approvals during 2001 for the treatment of

* 1

* 2

02N-0169

Ortec International, Inc.

TS5

treatment of Epidermolysis Bullosa and donor sites in burn patients, Ortec is also pursuing FDA approvals for venous and diabetic skin ulcers and is in the midst of clinical trials for these indications.

Our purpose in coming before this hearing is to express our strong opposition to any jurisdictional transfer of the regulation of wound healing products containing live cellular components from the Center for Devices and Radiological Health to the Center for Biologics Evaluation and Research.

[Question 1 is set out here only for reference purpose only]

- 1. What are the public health concerns related to these combination products as a whole and with respect to their individual components? What information should the agency require in the premarket submission to demonstrate the safety and efficacy of combination products that contain live cells used in combination with a device matrix for wound healing (e.g., wound repair, or skin regeneration, replacement or reconstruction)? What other issues are important (e.g., clinical trial design, informed consent, infectious disease concerns)?***

OrCel™ has been in clinical evaluation for acute and chronic wounds since 1992, and in commercial distribution since 2001 with no reports of serious adverse events directly related to the use of the product. All of the data from our controlled clinical evaluations have been reviewed by CDRH and demonstrates an excellent safety profile. Therefore, we see no need for a change in jurisdictional control as it relates to safety and efficacy of the current products under development or in commercial distribution.

* 3

The public is concerned with access to safe and effective treatments for severely compromising wounds arising from a variety of acute and chronic situations not with jurisdictional control. These combination products provide an immediate covering that helps reduce the risk of infection, protect against either fluid loss or desiccation, and helps to restore the skins natural functions through promoting and speeding the healing process.

We believe that the approach applied by CDRH under the current regulatory scheme is comprehensive for wound care products, including those containing live cells. CDRH provides adequate protection of the public health from the risks of transmission of communicable disease and from therapies and products that may be potentially dangerous to the public health. # 4

Since the Medical Device Amendments of 1976 the FDA has been working to clarify the classification of wound care products. Combination wound care products may be composed of any combination of a device, drug, or biological product. Under section 503(g) of the Food, Drug, and Cosmetics Act (the act), FDA must designate a Center within FDA to have primary jurisdiction over the premarket review. The policy, procedures, and guidance applied to date by FDA designate the primary jurisdiction over wound care products, including combination products containing live cellular components, to CDRH.

Throughout this process CDRH has provided guidance and expertise both through the review process and the development of specific guidelines. Their clinical and manufacturing expertise encompasses a myriad of indications including acute and chronic wounds, orthopedics, periodontal disease and other areas of repair, replacement, and regeneration of tissue.

In addition to their ability to regulate the biomaterials associated with wound healing products, CDRH has also demonstrated significant knowledge and scientific expertise in the regulation of human and animal derived cellular and extracellular products through years of jurisdictional responsibility. CDRH plays a key role in the development and implementation of critical FDA guidance documents and inter-center agreements that have a direct impact on establishing the safety and effectiveness of combination products containing live cellular components. These guidance documents adequately address the chemistry, manufacturing, and control requirements for cell therapy products, including recommendations for labeling claims, outcomes measures, clinical trial designs, and special considerations for preclinical development and testing. Specific public safety concerns addressed by these documents include the transmission of infectious agents (such as AIDS and hepatitis), contamination control (such as mycoplasma), toxicity, and Immunogenicity.

The autologous and allogeneic cells in combination with a device matrix for wound healing, unlike systemic or metabolic cell therapies to treat malignant and

infectious disease, create a local environment rich in growth factors, cytokines and extracellular matrices for wound healing. The clinical concerns regarding this type of wound healing device are more on a local level and center around risks of infection, the transmission of viruses or the potential for an immune response. To date, we are not aware of any serious public health issues arising from these combination products containing live cellular components. The safety and effectiveness issues have been adequately addressed in the premarket requirements and guidance documents and adequate controls are currently in place.

[Questions 2 and 3 are set forth for reference purposes]

- 2. Given that primary mode of action determines jurisdiction for combination products, what information should the agency consider in identifying the level of contribution of each component to the therapeutic effect of the product? For example, skin replacement products are intended to act as wound coverings (historically considered a device action), and as mediators of tissue regeneration or repair by providing a living substrate to grow replacement tissue and through the production of soluble factors (historically considered to be biological product activities). What information should the agency consider in determining which action is primary?***
- 3. In instances where both components of a combination product containing live cells appear to make a significant contribution to the therapeutic effect of the product and it is not possible to determine which mode of action is primary, what other factors should the agency consider in the assignment of primary jurisdiction? Is there a clear hierarchy among these additional factors that should be observed in order to ensure an adequate review? Should these same factors be used to determine the appropriate type of premarket application?***

5

The technological advances of the past 10 years have made possible products combining devices, pharmaceuticals, and/or biologics (Combination Products). Such products are likely to increase in importance and numbers over the next few years, and they represent a significant increase in level of complexity and scientific challenge to CDRH and FDA as a whole. Whether these products were regulated as devices or biologics has depended on the primary intended use of the product; however, there were no clear pathways or guidelines for regulating these products. The approach taken by CDRH has always included a degree of input from each regulatory Center, balancing safety and effectiveness with the desire for timely decisions. These products need to be regulated with an approach that embodies the philosophy of CDRH, one that is least burdensome, predictable, timely, flexible, transparent, interactive, and effective. CDRH has historically developed a plan of collaboration with other Centers for the evaluation of combination products.

Intended use, not the primary mode of action, should continue to be the critical factor in determining the jurisdictional control for these products. Wound healing is a complex process such that all of the factors involved, and the potential contribution of each factor to the healing process as a whole, have not been well defined. The wound healing products containing both non-living cellular matrix components (such as Type I collagen) and living cellular components (such as cytokines and growth factors) combine to create a local environment that is conducive to wound healing, repair, and regeneration by the host cells. It is

extremely difficult to determine which action is primary since the overall outcome is dependent on the total wound environment.

Since we believe that intended use is the critical factor that should determine the assignment of primary jurisdiction, the indicators that should be taken into consideration both in determining jurisdiction and the appropriate type of premarket approval should center on product safety and effectiveness and the FDA's adverse reporting process. CDRH has maintained jurisdictional responsibility over wound healing products since the Medical Device Amendments of 1976. Even as new technologies have emerged and the complexities of incorporating cellular or tissue-engineering components into wound healing products introduced new scientific challenges, CDRH has developed the necessary technical expertise either within the organizational structure of CDRH or through inter-center cooperation to meet statutory requirements and to bring new technologies to the market. CDRH has kept pace with the rapidly evolving technologies in wound healing products including the growing number of combination products. Overall, as an industry we have received more than adequate guidance from CDRH in regards to addressing the challenges of our technology, including critical technical expertise related to manufacturing, safety testing, and well-designed controlled clinical evaluations. The critical success factors associated with our commercialization are directly related to the oversight and guidance provided by CDRH.

6

Again, let me emphasize that the critical factor that should determine the jurisdictional responsibility of these products should be driven by the indications for use and the experience and expertise associated with risks presented to the public health by the clinical use of these products. CDRH must remain the lead center associated with the jurisdiction and control of these products in order to ensure the continued flow of safe and effective new technologies into the wound care portfolio to better serve the public.

* 7

Thank you for this opportunity to present Ortec's opposition to any jurisdictional changes to the regulation of combination products containing live cellular components.