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**Statement of Diana Zuckerman, Ph.D., President
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 At the FDA's Public Hearing on
 Combination Products Containing Live Cellular Components
 June 24, 2002**

Every year, a large number of patients require artificial skin products to aid their recovery -- including patients suffering from burns, diabetic cutaneous lesions, and traumatic injuries. The safety and effectiveness of these products are tremendously important to patients and their families. We look to the FDA to ensure that the interests of these vulnerable patients and their worried families will be paramount, as the agency determines the optimal manner in which to regulate these products.

We strongly believe that regulatory jurisdiction for combination products should be determined on a scientific basis, not on historical precedent. The most important questions are:

1. What is the optimal approach for determining the primary mode of action of these combination products?

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2. What is needed for the FDA to assure the safety and efficacy of these combination products in terms of pre-market review, post-market surveillance, and inspections?

Wound-Healing Combination Products

In assigning jurisdiction over the regulatory process for wound-healing combination products, primacy must be given to the specific characteristics of each product under consideration, rather than historical precedent. A Center should not be awarded jurisdiction over a combination product simply on the basis of its past jurisdiction over earlier products in the same category. The products being discussed today have advanced far beyond the simple wound coverings of yesteryear, and will continue to grow in complexity.

The complexity of these products are, with few exceptions, primarily attributable to their biologic component. For example, the complexity of Integra® resides primarily in its lower layer, which is composed of interwoven bovine collagen and carbohydrates. The porosity and biodegradation properties of this lower layer are crucial to the proper functioning of the product. In contrast, the upper

layer consists of a relatively simple silicone sheet that is removed after a period of healing.

Future products may incorporate growth factors, cytokines, angiogenic agents, and even genetically modified cells. Living cells are already key components in some wound-healing products (e.g. EpicelTM, which utilizes cultured human keratinocytes), and are likely to play an even greater therapeutic role in the future. With the increased use of biologic components comes an increased need for vigilance against potential complications -- e.g. infection, inadequately controlled cellular growth, and rejection -- that may arise from biologic products.

The Optimal Approach for Determining the Primary Mode of Action

We believe that the primary mode of action should determine jurisdiction for combination products. The pertinent issue is how the FDA should evaluate the components of a combination product to determine its primary mode of action. For any combination product, jurisdiction should be based on an objective evaluation of every new product.

Most wound-healing combination products rely primarily on their biologic components for therapeutic effect. There is a distinct trend in the field away from producing relatively simple wound coverings that act as temporary physical barriers and towards permanent, biologically interactive products that actually promote healing and regeneration. With those factors in mind, an objective evaluation of each new combination product should include the following criteria:

1. Which component of a combination product is most interactive with the human host?

If we take the example of Integra®, its unique properties rest almost entirely in its lower, biologic layer. Composed of a matrix of interwoven bovine collagen and glycosaminoglycan carbohydrate molecules, the lower layer is designed to coax the host's surviving fibroblasts and other supporting cells into regenerating a dermal layer of skin.

2. Which component is most complex in design and structure?

Again taking the example of Integra®, the upper silicone layer is not nearly as complex in

structure and design as the biologic lower layer which incorporates complex protein and carbohydrate molecules. Needless to say, living cells and tissues are far more complex in design and structure than any inorganic component.

3. Which component requires a more complex production and manufacturing process?

A more complex production and manufacturing process makes it more difficult to maintain quality assurance standards. As an example, one can turn to the difficulty in culturing living cells. Even small changes in procedures related to nutritional media, antigen quantity, incubation temperature, and infection control may seriously affect the safety, efficacy, viability, and stability of cultured cells. Another example is the precise production controls needed to regulate the porosity and biodegradation properties of Integra's® lower biologic layer. It seems likely that in nearly all cases, regulating the production and manufacture of biologic components will pose a more serious challenge than regulating the production of non-biologic components.

4. Which component has the most potential for producing serious complications?

The increased incorporation of biologic components in medical products poses the threat of introducing new and serious complications seldom seen in the past. For instance, the use of living cells could result in the introduction of viral contaminants. Some future products incorporating living cells may need to be carefully monitored for adequate cellular growth and reproduction control. The antigenicity of biologic components needs to be carefully tested and controlled to prevent rejection and the induction of autoimmune disorders.

Essential Capabilities for a Center Regulating Wound-Healing Combination Products

In light of the important role of biologic components in wound-healing combination products, it seems reasonable that in most cases the FDA should assign jurisdiction to the center best suited for evaluating biologic products. Ideally, such an agency would have in-house expertise in molecular cell biology, infectious disease, immunology, genetics, and embryology. Such expertise will also be invaluable in addressing concerns regarding perceived threats like bovine spongiform encephalopathy (mad cow disease).

As noted earlier, the increased complexity of future wound-healing combination products will almost certainly be attributable to their biologic components. Jurisdiction should be assigned to the center that is most capable of addressing the 4 criteria mentioned above.

Finally, the center assigned jurisdiction over these combination products should be provided adequate regulatory authority and sufficient resources to ensure the safety and efficacy of these products. The designated center should have a demonstrated commitment to well-designed post-market surveillance studies as well as the authority to require such studies and to impose civil monetary penalties and other sanctions against manufacturers who fail to complete such studies. Sufficient resources must be provided, preferably through appropriations, that allow the hiring and retention of personnel with expertise in relevant fields in biology and medicine. Resources must be provided to ensure adequate staffing for facility inspections and adverse event monitoring. We have strong concern that any centers that are having difficulty in meeting the staffing requirements for inspections and adverse event monitoring should not be given the additional burden of regulating these complex combination products.