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AdvaMed's Written Testimony at FDA Public Hearing: on Combination Products Containing Live Cellular Components

by
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I. Introduction

I am Carolyn Jones, Associate Vice President in the Technology and Regulatory Affairs Department of Advanced Medical Technology Association, more commonly known as "AdvaMed." AdvaMed is the largest medical technology association in the world, representing more than 1,000 innovators and manufacturers of medical devices. One of AdvaMed's principal roles is to support and facilitate laws and policies that will bring safe and effective innovative technologies to market expeditiously.

On behalf of our members, we come before this hearing to express strong opposition to any jurisdictional transfer of tissue-engineered wound products, historically reviewed and regulated by the Center for Devices.

While the narrow topic today is jurisdiction of wound healing products containing live cells, AdvaMed and its members are concerned that any jurisdictional decisions made in this area also may impact other extracellular wound healing and related structural/repair products. A number of AdvaMed's members are developers of innovative technologies in the wound healing area, who believe that device status is critical to continued successful development of these products.

As I will discuss in my presentation, AdvaMed and its members do not support a shift in jurisdiction of wound healing products containing cellular components, for four principal reasons:

- First, there is no public health concern with the products being considered today; indeed, the products provide important public health benefits, which should be supported by efficient pathways to market;

- Second, premarket data uncertainties, if any, can be addressed through guidance, and do not require a sweeping jurisdictional change to accomplish this objective;

- Third, CDRH regulatory initiatives have facilitated the development and marketing of these important products in their long pathway to market, and a change in jurisdiction would create new regulatory burdens, uncertainties and costs; and

- Finally, we believe there are legal, regulatory, and practical impediments to a jurisdictional change.

[Question 1 is set out for reference purposes.]

FDA's Question 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 regulatory requirements

are necessary to ensure that adequate manufacturing controls are in place for both the device and live cell components? What other issues are important (e.g., clinical trial design, informed consent, infectious disease concerns)?

II. Public Health Considerations

In considering the Federal Register's various inquiries, the Agency's very first question suggests that there are, or may be, public health concerns with this category of products, and that these public health concerns might be one reason why a jurisdictional transfer is needed. AdvaMed is unaware of any public health issues presented by tissue-engineered wound products that have been reviewed and approved by CDRH. To the contrary, these products have had an excellent premarket and postmarket safety profile. Moreover, tissue-engineered wound healing products have been recognized as having extremely important public health benefits.

CDRH has recognized these many benefits. In CDRH's recent annual reports, it cited wound healing products such as Apligraf®, Orcel®, and Dermagraft® as important "advances in patient care" and "significant medical technology breakthroughs," and, in recognition of their importance, has sought to facilitate their pathways to market.

There is no public health reason compelling a shift in jurisdiction for this category of products, while the public health need for them is clear. We believe innovation will be fostered by continuing CDRH review.

III. Premarket Review Requirements

A second theme raised in the Agency's Federal Register notice is uncertainty regarding premarket review requirements for these products.[1/] The Notice seems to suggest that premarket data uncertainties could be solved by a shift in jurisdiction.

AdvaMed believes that good guidances, and not jurisdictional changes, are the most appropriate way to address any premarket data questions or confusion. CDRH historically has shown a willingness to issue guidances, with hundreds of guidances issued by the Office of Device Evaluation alone. Industry has found these documents—when drafted pursuant to good guidance practices—to be very effective in clarifying premarket data requirements applicable to its products.

We note that, for many of the products covered by this hearing, FDA already has existing draft multi-center guidance (Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment),[2/] that addresses premarket requirements. All three Centers participated in the development of this guidance, and accepted the preclinical and clinical

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1/ "[S]uccessful development and marketing of these products may be slowed by uncertainty about jurisdiction, particularly as it relates to the nature and scope of regulatory requirements that must be met in order to bring these products to market." 67 Fed. Reg. 34722 (May 15, 2002).

2/ FDA, Chronic Cutaneous Ulcer and Burn Wounds (Draft, June 2000).

considerations discussed in that document. By its terms, each Center will implement the guidance, and, since its issuance, our members report that CDRH has used the guidance very ably in its reviews.

CDRH also is involved in outreach initiatives that allow its reviewers to keep abreast of new technology and work with industry on applicable national and international standards in the tissue engineering, orthopedic, wound repair, and related fields—to ensure that data requirements are appropriate and clear. CDRH works regularly, for example, with national and international standard-setting organizations, such as the American Society for Testing and Materials ("ASTM") on tissue engineering standards, and CDRH officials have served as Board and committee members of this organization. These types of CDRH outreach initiatives have enabled reviewers to better understand new technologies, in a way that has fostered commercialization of innovative products.

There are also other premarket review reasons why CDRH should retain jurisdiction. For one, the Center for Devices has extensive experience in the wound healing area. It has reviewed a wide variety of cellular and extracellular wound healing products over the years, and its expertise has evolved with the technology. Additionally, CDRH has the specific clinician expertise important for applications of these products—for example, clinical expertise in the orthopedic, dental, and related wound repair areas—areas that historically have not required extensive involvement by CBER.

Finally, combination products do not prevent, and in fact encourage consultation, as necessary, to address any gaps in knowledge or experience.[3/] The statute and regulations both speak directly to the consultation process, and, as you know, reforms are also underway to further improve this process.

Therefore, to the extent that there are uncertainties or questions relating to the type or scope of data that should be required for these products, AdvaMed believes these issues should be addressed through new guidances or modification to existing guidances. Attempting to resolve any specific data issues by implementing a sweeping jurisdictional shift will only create significant new regulatory burdens for industry. New regulatory burdens would slow the path to market far more significantly than any data uncertainties cited in the Federal Register.

IV. Importance of CDRH Regulatory Initiatives

Other issues of importance to our members are the CDRH premarket review initiatives that have been used to bring these innovative wound healing products to market. Our members indicate that, given the significant premarket data requirements that exist for

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3/ See Section 503(g)(2) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 353(g)(2) (stating "[n]othing in this subsection shall prevent the Secretary from using any agency resources of the Food and Drug Administration necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article"); 21 C.F.R. § 3.4(b) (noting that "[t]he designation of one agency component as having primary jurisdiction . . . does not preclude consultations by that component with other agency components . . .").

this class of products, CDRH premarket review initiatives have been critical to making these products available.

The various initiatives which they relied on include: least burdensome review, early collaboration meetings, 100-day PMA meetings, and interactive procedures—all of which were implemented pursuant to the Food and Drug Administration Modernization Act—and modular PMAs and real-time labeling reviews—implemented pursuant to CDRH reengineering initiatives.

Recently, several of our member companies also have been availing themselves of humanitarian use device mechanisms, to allow earlier patient access to their technology. Ortec has made dermal replacement products (Orcel) available to children with a rare skin disease called epidermolysis bullosa or EB, for the treatment of hand deformities; we understand that Advanced Tissue Sciences is pursuing a more general EB indication for its Dermagraft product; and Genzyme has pursued an HUD strategy for Epicel™, for use in certain patients with deep dermal or full thickness burns.

The HUD program exempts products intended to benefit persons with rare diseases or conditions from extensive clinical studies, and, thus, makes these products available more quickly to those who need them. There is no comparable program to this in the Center for Biologics.

These many device initiatives are the result of not just one, but several statutory amendments, and legislative reform is expected to continue to respond to and foster innovation. By contrast, the statutory authority for biologics has evolved more slowly and infrequently over the years.

CDRH's External Science Review Subcommittee, chaired by Dr. Robert Nerem, who is speaking here today, concluded that "combination 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."[4/] The CDRH philosophy and practices have served the public well with respect to the wound healing products being discussed today, and AdvaMed strongly supports continued retention of device processes, authorities, and personnel.

V. Primary Mode of Action Determinations

FDA's next questions in its Federal Register notice focus on the interpretation of "primary mode of action" and factors that should be considered in determining primary jurisdiction.

4/ Science at Work in CDRH: A Report on the Role of Science in Regulatory Process (Nov. 16, 2001) (emphasis added).

[Questions 2 and 3 are set out for reference purposes.]

FDA's Questions 2 and 3: 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? What information should the agency consider in determining which action is primary?

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?

A. Interpretation of Primary Mode of Action

These questions suggest that there already exists a definition or policy interpretation of "primary mode of action" that is based on the "level of contribution of each component to the therapeutic effect of the product." Historically, the FDA has not interpreted "primary mode of action" in this way, and we understand this to be a relatively new concept that appears only to have surfaced in informal FDA discussions leading up to this meeting. AdvaMed strongly opposes use of this new interpretation in determining "primary mode of action" for several reasons.

FDA's proposed interpretation appears to require the evaluation of the constituent parts of these products, which is largely unworkable for this class of products. The wound healing products under consideration are integrated products without clearly segregable components. These combination products are not like drug-eluting stents or laser-activated pharmaceuticals. Bear in mind here that all of the components of these wound products (that is, the synthetic, the extracellular, and the live cell components) work together to serve the same essential function of facilitating wound healing. It would be virtually impossible, and financially impractical, to tease out the level and type of contribution of synthetic and extracellular vs. cellular components, using current methodologies.

Instead, FDA and sponsoring companies quite properly have looked historically to the role of the combined product—the integrated whole. They have concluded that—as a whole—the product serves as a replacement for the damaged skin in the wound bed. Like non-interactive wound dressings, they primarily provide a restoring environment for the wounds to heal, although they are augmented with cellular components, to facilitate the wound dressing's functionality. The functions of the combined product, thus, very clearly meet the historical definition of device.

B. Legal Considerations

There are also legal impediments to the proposed interpretation of primary mode of action. From our initial legal review of these issues, there are at least four concerns that the Agency will need to address:

1. Administrative Law Considerations

First, as I just mentioned, FDA regulations and policies have looked historically to the intended function of the combined product—not to the relative contribution of each component. Both the statute and regulations at Part 3 refer to "primary mode of action of the product," and do not refer to its components.

Consistent with this authority, FDA's policy historically has considered the primary mode of action or function of the combined product, rather than its constituent parts, and, thus, the new language used in the Federal Register is at odds with various guidances that the Agency has issued in this area. For example, one important theme in the CDRH-CDER Intercenter Agreement is that combination products that have primarily a structural, physical, or reconstruction purpose are regulated as devices.[5/] CBER also historically has supported this application of the definition of device in its proposed framework for regulation of cellular and tissue-based products. That document states: "[t]issue-based products that are intended for diagnosis or therapeutic effect by physical action (including reconstruction or repair), and that contain synthetic or mechanical components, and achieve their primary mode of action by means other than metabolic or systemic action, are regulated as devices by CDRH."[6/] Likewise, in the CBER-CDRH Intercenter Agreement, it is expressly acknowledged that "cultured skin will be regulated by CDRH under the Medical Device Authorities."[7/]

Also, past practices—in addition to regulations and policies—consistently support the interpretation of primary mode based on primary intended function of the combined product. For more than a decade, companies developing technology in the wound healing area have relied on the FDA's historical interpretation, in planning their development and regulatory pathway activities. Not just wound healing products, but also a wide variety of other extracellular products have been granted device status based primarily on their structural, replacement, and repair functions.

5/ An "implant, including an injectable material, placed in the body for primarily a structural purpose even though such an implant may be absorbed or metabolized by the body after it has achieved its primary purpose will be regulated as a device by CDRH." Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991).

6/ FDA, Proposed Approach to Regulation of Cellular and Tissue-Based Products (Feb. 28, 1997).

7/ FDA, Intercenter Agreement Between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991).

AdvaMed is concerned that a new interpretation could affect not just the products that are the subject of this hearing, but a wide variety of other tissue-derived extracellular products regulated by CDRH.[8/] Because these changes in jurisdiction could have enormous, detrimental impact on affected entities, and alter how or even whether they do business, AdvaMed believes that such changes would have the force and effect of a substantive rule, requiring notice and comment.

Although we appreciate these stakeholder meeting opportunities to convey our concerns directly to Agency decision-makers, we believe there must be administrative protections in place that require on-the-record responses to industry's important concerns. These on-the-record processes also will enable review by other entities, such as the Department of Health and Human Services, OMB, and the courts, as necessary.

2. Part 3 Considerations

Relatedly, we note that FDA jurisdictional regulations and philosophy provide that, for products designated for review by a particular Center, the Agency may not change that Center, except for "public health or . . . other compelling reasons."[9/] While certain of the products being considered today may not have undergone a formal designation process, others have—and, in any event, the same principle necessarily applies to all products affected by this hearing. Like companies that have received formal designations, all companies subject to this hearing have relied on the Agency's interpretation to build their premarket development strategies, their markets, and their business. Without a public health or other compelling reason—which we believe the Agency has not conveyed, and cannot supply—jurisdiction of these products should remain within CDRH, consistent with Part 3 of the regulations.

3. Statutory/Definitional Concerns

As a third point of concern, AdvaMed also believes that Agency lawyers will need to grapple with statutory constraints presented by the definition of "biological product." Unlike the definitions of "device" and "drug," which are fashioned primarily around intended use, the definition of "biological product"—as you know—is specifically defined by substances (i.e., viruses, therapeutic serums, toxins, antitoxins, blood components or derivatives, allergenic products, and analogous products). This list of substances does not include structural cellular products in the mix, and the legislative history of the Public Health Service Act, as well as case law, suggest that tissue and cellular products would be regulated separately, and not under the definition of "biological product."

8/ These include: other human fibroblast-derived skin substitutes; bovine-derived skin substitutes; porcine-derived protein matrices for periodontal use; bovine-derived hydroxylapatite matrices containing synthetic peptides for periodontal use; surgical patches comprised of bovine-derived pericardium; collagen materials containing bone morphogenic proteins for spinal fusion indications; and demineralized bone products.

9/ 21 C.F.R. § 3.9.

These definitional constraints will need to be dealt with in any contemplated jurisdictional change. Where the Public Health Service Act does apply—those aspects of the law that relate to protection against disease transmission—tissue-engineered wound products, as well as other products currently regulated by CDRH,[10/] remain subject to the requirements of registration, donor screening, and Good Tissue Practices, once finalized.[11/]

4. Cost-Benefit Directives

Finally, FDA has long recognized, under Executive Order 12866, that it should evaluate and weigh all costs and benefits of alternative regulatory approaches in order to select those approaches that maximize net benefits (including potential economic, public health and safety, and other advantages).[12/] AdvaMed believes that any shift in jurisdiction of tissue-engineered products must be evaluated for costs and benefits.

As we have said, CDRH has established very capable expertise, and significant invested knowledge in both the technology and the clinical disciplines applicable to this technology. We can identify no public health or other compelling benefit from transfer of jurisdiction and, in fact, industry remains uncertain as to what the Agency's perceived reasons and benefits for this proposal might be, since there is no discussion of this issue in the Federal Register. If the availability of user fees for biological products is a factor in the proposed transfer of jurisdiction, ongoing legislative efforts indicate that this distinction from CDRH is likely to be short-lived.

Although AdvaMed acknowledges that CBER has extremely able scientists, we believe that a Center's premarket approach is driven by the primary laws, regulations, and policies that the Center administers. Practically speaking, it is awkward for CBER reviewers charged primarily with administering one set of more rigid regulations—to be expected then to switch gears for an isolated few device products, and apply a different set of regulations, programs, and initiatives that have taken years for CDRH itself to adopt, absorb, and apply effectively.

A second jurisdictional suggestion we have heard—would be to leave alone those products already approved or reviewed by CDRH, but to make the jurisdictional switch prospectively.

In this case, an extremely important factor that FDA should consider in determining primary mode of action is whether the same product is already approved or cleared by a particular Center for a different use. Important to all companies is consistency of regulation with respect to product development strategies, premarket development and testing programs, and postmarket compliance plans. To develop additional, separate regulatory systems for a product (from those already in place), would require a

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10/ Such products include, for example, bone void fillers containing demineralized bone in a synthetic carrier.

11/ Section 264 of the Public Health Service Act, 42 U.S.C. § 361.

12/ Executive Order 12866 (Sept. 30, 1993).

substantial investment of resources, time and personnel, that is likely to hinder future product development for most companies.

Moreover, the requirement to have two different quality systems for the same product would present major logistical and compliance challenges and confusion. AdvaMed understands, for example, that the requirement to have two different quality systems has compelled some companies in the IVD context, to build separate manufacturing facilities, in order to avoid the logistical and compliance challenges between its products regulated by CBER, and those regulated by CDRH. Given these burdens, there would seem to be no good reason to have two different sets of quality systems.

VI. Conclusions

Combination products containing live cellular components have been regulated by CDRH for a decade, without any public health, premarket, or manufacturing concerns, and the mechanisms afforded under CDRH jurisdiction have fostered innovation of these products. It has been reported that over 60 companies are involved at some level in the development of tissue-engineered products. Only four of these products have been approved—and we believe it is no small coincidence that all four of them have gone through CDRH and device premarket mechanisms. To sustain innovation in this area of importance to the medical and patient communities, regulatory cycles need to be matched with product life cycles. The burdens to market are already severe enough. We, therefore, strongly urge the Panel and FDA to avoid a jurisdictional shift that ultimately will further slow, and perhaps irreparably impair, the successful development and commercialization of these important tissue-engineered wound healing products**.**

Thank you for your attention.