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Re: Legal Concerns with Proposed Jurisdictional Changes to Combination Wound Repair Products Containing Live Cellular Components

Dear Mr. Troy:

On behalf of our member companies, we are writing to convey legal concerns regarding a potential change in Center jurisdiction for combination cellular wound repair products that have been regulated for over a decade by the Center for Devices and Radiological Health ("CDRH"). AdvaMed is the largest medical technology association in the world, representing more than 800 innovators and manufacturers of medical devices. As internal Agency documents will confirm, the majority of requests for designation and product jurisdictional debates involve device issues and, consequently, combination product issues are of the foremost importance to our membership.

On May 15, 2002, the Food and Drug Administration ("FDA") issued a notice in the Federal Register, announcing a public hearing to discuss the "jurisdictional classification, assignment, and premarket review of certain products that consist of living human cells in combination with a device matrix."[1/] The announcement further stated that the hearing would focus on products that are intended for wound healing, and that the Agency was soliciting information to determine whether this class of products that had been regulated by CDRH, should be transferred to the Center for Biologics Evaluation and Research ("CBER") for premarket review and regulation.

At a Part 15 hearing, held June 24, 2002, AdvaMed made an oral presentation conveying its strong opposition to a shift in product jurisdiction, for scientific, policy, and legal reasons.[2/] Affected companies currently subject to CDRH jurisdiction made similar presentations

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1/ 67 Fed. Reg. 34722 (May 15, 2002).

2/ See Attachment 1.

opposing the move.[3/] Because members of the Panel requested further explanation of the several legal concerns expressed by AdvaMed as part of its remarks, we have refined those concerns, and have presented them in this letter to you. Although a number of compelling policy points also were made by AdvaMed, in the interest of brevity, we have confined this communication simply to legal issues, but encourage your review of our other comments at Attachment 1. Following your review of this correspondence, AdvaMed requests a meeting with your office, to further discuss the issues we have raised, and to consider appropriate next steps.

I. Overview

As briefly discussed in our testimony at the June 24 meeting, AdvaMed's principal legal bases for opposing any jurisdictional shift for wound repair products containing live cellular components, are as follows:

- First, FDA's newly articulated proposal on "primary mode of action" -- the basis for jurisdictional decisions -- departs fundamentally from past policy pronouncements and practices; imposes profound costs and other adverse consequences on affected entities; and, consequently, requires notice-and-comment rulemaking pursuant to the Administrative Procedure Act ("APA");

- Second, the jurisdictional shift for this class of products is inappropriate under the statutory definition of "biological product" and related licensure authority;

- Third, there are also jurisdictional constraints to regulation of these products under device authorities;

- Fourth, before a shift in jurisdiction of this type, the Agency must demonstrate a strong public health or other compelling basis for the change, and this has not occurred; and

- Finally, Executive Order 12866 and related requirements, which direct FDA to consider all costs and benefits of significant regulatory actions prior to their adoption, have not been considered, and, once considered, will show costs significantly outweighing advantages.

3/ See Docket No. 02N-0169, Combination Products Containing Live Cellular Components.

Provided below is a full discussion of these concerns, in the order presented.

II. Concerns With FDA's Newly Articulated Proposal on "Primary Mode of Action"

The Federal Register notice announcing the Part 15 public hearing included the following question for stakeholder discussion:

> "Given that primary mode of action determines jurisdiction for combination products, what information should the [A]gency consider in identifying the level of contribution of each component to the therapeutic effect of the product?"[4/]

This and related questions in FDA's Federal Register notice appear to assume 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."[5/] AdvaMed is concerned with this reference, and believes the newly articulated interpretation of "primary mode of action," is inappropriate, for three reasons:

- the interpretation fundamentally departs from the Federal Food, Drug, and Cosmetic Act, FDA regulations, and FDA policy pronouncements and practices;
- a change of interpretation, such as that proposed by the Federal Register, would impose profound costs and other adverse consequences on the affected industries; and
- because the Federal Register's proposed interpretation represents a change in FDA's historical interpretations and practices, and because the change in interpretation, if implemented, will profoundly affect industry, the Agency must proceed through notice-and-comment rulemaking pursuant to the Administrative Procedure Act.

A. The Proposed Interpretation Fundamentally Departs from the Federal Food, Drug, and Cosmetic Act, FDA Regulations, FDA Policy Pronouncements, and Precedents

The Agency's proposed interpretation that "primary mode of action" be determined based on "the level of contribution of each component," is not a concept found in applicable

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4/ 67 Fed. Reg. at 34723.

5/ Id.

provisions of the FFDCA or FDA regulations,[6] the respective legislative and regulatory histories of these provisions,[7] FDA policy pronouncements, or past FDA practices, and in fact represents a fundamental departure from the Agency's prior interpretation of this term. The starting point for understanding FDA's historical interpretation of "primary mode of action" begins with the statute itself, which directs the analysis to the composite product and not its components, by requiring the FDA to "determine the primary mode of action of the combination product."[8] Consistent with this mandate, and from a decade of interpretation, two important guiding principles have emerged. First, it is clear from FDA's regular reaffirmations in policy pronouncements and precedents, that the Agency looks to the product as a whole to assess the primary mode of action. Secondly, as described below, we know from both guidance and precedents, that the term "mode of action" has been interpreted not as "mechanism of action," but, rather, as primary intended function of the combined product. Consequently, until the May 15, 2002 Federal Register notice, industry was unaware that "primary mode of action" would be examined, based on a new and significantly different standard of "relative contribution of each component."

Both Intercenter Agreements and CBER cellular and tissue pronouncements, direct industry to look to the intended function of the combined product rather than its constituent parts. A principal important theme in the CDRH-CDER Intercenter Agreement, is that combination products that have primarily a structural, physical, or reconstruction purpose, should be regulated as devices. For example, the Agreement states that "[a]n 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."[9] CBER also historically has employed this functional approach to interpreting "primary mode of action." In CBER's proposed framework for regulation of cellular and tissue-based products, it 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

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6/ Section 503(g) of the FFDCA provides that, in determining whether a combination product shall be reviewed as a drug, device, or biological product, the "Secretary [FDA] shall determine the primary mode of action of the combination product." 21 U.S.C. § 353(g) (emphasis added). Similarly, FDA's regulation on product jurisdiction, 21 C.F.R. § 3.4, states that "the agency shall determine the primary mode of action of the product" (emphasis added). See also 56 Fed. Reg. 58754, 58754 (Nov. 21, 1991) (stating only that "[t]he designation is to be made based upon a determination of the 'primary mode of action' of the combination product") (emphasis added).

7/ Neither the legislative history of this provision, enacted as part of the Safe Medical Devices Act of 1990, nor any other provision of the FFDCA, provides any additional explanation or discussion of "primary mode of action."

8/ Section 503(g) of the FFDCA, 21 U.S.C. § 353(g) (emphasis added).

9/ FDA, Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991) (emphasis added).

as devices by CDRH."[10/] Likewise, in the CBER-CDRH Intercenter Agreement, in recognition of the structural/replacement function of cultured skin, the Agreement expressly acknowledges that "cultured skin will be regulated by CDRH under the Medical Device Authorities."[11/] Each of these policy statements, thus, refers to the structural, restorative, or replacement mode of action -- the primary intended function -- of the combined product, rather than to the relative contribution of the component parts.

Past Agency practices, in addition to regulations and policies, also consistently support the interpretation of "primary mode of action" based on primary intended function of the combined product. Over the past decade or more, CDRH has granted device jurisdiction to a long list of products based on the primarily physical, structural, restorative, repair, and/or replacement function of the combination as a whole. Examples of products that contain live cells, proteins, and other extracellular components with biological characteristics, but which have been deemed to have primarily device functions, include the following: demineralized bone paste products; spinal fusion products; porcine-derived protein matrices for periodontal repair; surgical patches composed of bovine-derived pericardium; skin replacement products containing extracellular components; tissue grafts; bone cements; and wound dressings.[12/] Labeling for these products, provided at Attachment 2, consistently supports that they have been deemed devices because of their intended structural, restorative, repair, and/or replacement purposes.

Consistent with this primary mode of action analysis, tissue-engineered wound repair products have been granted CDRH jurisdiction and effectively have been regulated as devices for a decade or more. There have been important premarket approval applications ("PMAs") approved and publicized by CDRH, and many more Investigational Device Exemption applications ("IDEs") filed for these products, based on the long-held understanding that the products serve primarily a structural/repair/replacement function.

Again, a review of labeling for those that have been approved, all of which are described as dermal or skin replacements, clearly evidences this structural/repair/replacement orientation.[13/]

Finally, these are not the only examples that can be provided to support past Agency interpretive practices. Many, if not most, other combination products that have been granted CDRH review over the years -- from combination bandages, to catheters with drug components, to dental devices containing fluoride -- have received device jurisdiction by virtue of their primary intended structural, physical, restorative, replacement, and/or repair

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

11/ FDA, Intercenter Agreement between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991) (emphasis added).

12/ See Attachment 2.

13/ See Attachment 2.

functions.[14/] Whether the Agency believes, in retrospect, that a "relative contribution of each component" standard legitimately could be applied to these products, is irrelevant; historically, they were not determined to be devices based on that analysis.

B. The Proposed Interpretation Would Impose Profound Costs and Other Adverse Consequences on Affected Companies

In reliance on the long history of regulation of these products under device authorities, manufacturers of structural cellular wound repair products have invested considerable resources for many years into device-related systems, and any alteration of that status would in essence change their entire structure and framework for doing business. During the June 24 meeting, entities currently regulated by CDRH, described the detrimental impact that a shift in jurisdiction would have, both on individual companies and on the direction of this industry. Many companies reported that their systems, personnel, development strategies, compliance programs, and marketing apparatus, all of which have been oriented around device requirements, would require a substantial investment of funds to reorient. Still others complained that, for tissue-engineered products already marketed as devices, the proposed shift could subject them to two or possibly three sets of premarket and postmarket regulations, including good manufacturing practice regulations, for the same technology. Given this substantial impact on affected companies, some of the speakers at the Part 15 hearing even expressed concern about the very survival of their companies, if a jurisdictional shift were to take place. The unambiguous message from the Part 15 meeting, then, was that of profound adverse consequences, should this change go forward.

It was also explained at the June 24 meeting that the proposed interpretation of "primary mode of action" presents significant concerns from a scientific and technological perspective. Both manufacturers of cellular wound repair products and independent researchers testified that cellular wound repair products are by structure and function single entity products, not clearly divisible, and applied as a whole to a designated wound site. Given the complexities of the body's wound healing mechanisms, the consensus view was that it would be difficult, and cost-prohibitive, to parse out the relative contributions of each of these products' components -- the contribution of the synthetic and extracellular components on the one hand versus the cellular components on the other. Thus, the proposed "relative contribution" standard, in the view of industry and researchers most affected, would present severe practical concerns as applied to cellular wound repair products.

14/ Other examples include drug-eluting stents; bone cement containing antimicrobial agents; cardiac pacemaker leads with steroid-coated tips; condoms, diaphragms, or cervical caps with contraceptives or antimicrobial agents; and dental wood wedges with hemostatic agents.

Moreover, it also was pointed out that all wound dressings -- interactive or otherwise -- have effects on the body's wound healing process at some level. By way of example, it is not uncommon for non-interactive wound dressing products, which contain collagen and other macromolecules -- but not live cells -- to be described as providing a natural scaffold that attracts whole cells and supports tissue remodeling.[15/] This example highlights the seemingly arbitrary delineation that the Agency is attempting to make between live cell and other wound products. AdvaMed is therefore 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.

C. A Change in FDA's Historical Interpretation Requires Notice-and-Comment Rulemaking

There are two reasons why notice-and-comment rulemaking is needed with respect to the Agency's newly articulated proposal on "primary mode of action:" (1) persons and entities outside the Agency are substantially affected by the proposal; and (2) the proposed interpretation departs fundamentally from the Agency's existing interpretation of this standard, relied on by industry for many years.

1. The proposal substantially affects outside interests.

Although Agency officials have suggested publicly that the proposed shift in jurisdiction is primarily for Agency management/resource purposes,[16/] the impact on affected companies, as described above, is nonetheless substantial. Case law holds that the exception from APA notice-and-comment proceedings for matters "relating to agency management or personnel"[17/] must be narrowly construed,[18/] and would not apply when "outside individuals are substantially affected."[19/] The U.S. Court of Appeals for the D.C. Circuit has stated that

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15/ See Cook press release dated January 24, 2000. See also HeliDerm™ Collagen Wound Dressing (K990086); Promogran Matrix Wound Dressing (K014129); Fibracol Plus Collagen Dressing with Alginate (K982597).

16/ See "CBER Tissue Products Office to be Established by Oct. 1," M-D-D-I Reports ("The Gray Sheet"), June 3, 2002, at 6 (discussing the administrative value of the new office, and announcing that the purview would include "the future of tissue engineering").

17/ 5 U.S.C. § 553(a)(2).

18/ Stewart v. Smith, 673 F.2d 485, 506 (D.C. Cir. 1982) ("the [agency management and personnel] exemptions [from notice-and-comment rulemaking] were ... to be narrowly interpreted"); Sanjour v. EPA, 786 F. Supp. 1033 (D.D.C. 1992), aff'd, 984 F.2d 434 (D.C. Cir. 1993).

19/ Id.; Joseph v. U.S. Civil Service Commission, 554 F.2d 1140, 1153 n.23 (D.C. Cir. 1977); Sanjour v. EPA, 786 F. Supp. 1033 (D.D.C. 1992), aff'd, 984 F.2d 434 (D.C. Cir. 1993); Seaboard World Airlines, Inc. v. Gronouski, 230 F. Supp. 44 (D.D.C. 1964).

"the burden of notice and comment procedures is warranted where a policy raises broad public concerns and has ramifications well beyond the confines of the agency involved."[20/] We, therefore, caution the Agency that any characterization of the proposal as a mere management issue would unfairly and improperly trivialize the adverse consequences expected for companies involved. Indeed, the Agency's decision to hold a Part 15 hearing on cellular wound repair products, and the vocal opposition to jurisdictional changes expressed at that hearing, are clear recognition that these particular jurisdictional issues involve far more significant concerns and controversies.

We also note that, while we appreciate Part 15 stakeholder meeting opportunities to convey our concerns directly to Agency decision-makers, we believe these hearings alone are not sufficient. We believe that 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 of decisions and decisional bases by other entities, such as the Department of Health and Human Resources, Office of Management and Budget, and the courts, as necessary.

2. The proposed interpretation is a fundamental departure from the FDA's historical interpretation

A second reason that rulemaking is needed, relates to the change contemplated by the Agency. As described above, the statements in FDA's May 15 notice regarding the "level of contribution of each component," represent a fundamental departure from FDA's historical interpretation of its statute and regulation.

Case law supports that any change in an agency's longstanding interpretation of its regulations that has been relied upon by the regulated industry, must proceed through notice-and-comment rulemaking pursuant to the APA. Several cases decided in the U.S. Court of Appeals for the District of Colombia over the last few years uphold the principle that notice-and-comment rulemaking is required when an agency departs from its historical interpretation of its regulations. For example, in Alaska Professional Hunters Association v. Federal Aviation Administration, the U.S. Court of Appeals for the D.C. Circuit held that, "[w]hen an agency has given its regulation a definitive interpretation, and later significantly revises that interpretation, the agency has in effect amended its rule, something it may not accomplish without notice-and-comment."[21/] A similar conclusion was reached by the court in Shell Offshore, Inc. v. Babbitt, which held that the Department of Interior's attempt to change its interpretation of its regulation on use of FERC tariff rates in a policy letter, must

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20/ Stewart v. Smith, 673 F.2d 485, 506 (D.C. Cir. 1982).

21/ 177 F.3d 1030, 1034 (D.C. Cir. 1999). See also Paralyzed Veterans of America v. D.C. Arena, 117 F.3d 579, 586 (D.C. Cir. 1997) (stating that "[o]nce an agency gives its regulation an interpretation, it can only change that interpretation as it would formally modify the regulation itself: through the process of notice and comment rulemaking").

proceed through notice-and-comment rulemaking. Although, in that case, the initial Department action was simply an interpretive policy, the subsequent change in interpretation was deemed "a new substantive rule ... [that] the agency is obliged, under the APA, to submit ... for notice and comment."[22/]

Two themes emerge from these rulings. First, the courts have not required that an agency's initial interpretation of its regulation be in the form of a written document for it to be considered definitive.[23/] Where regulated entities have relied, and based their businesses, on longstanding agency regulatory interpretations -- however informally those interpretations are expressed, or however informally those agency actions were taken -- the courts have held that the interpretations necessarily become authoritative administrative positions, and that any revision of those interpretations require notice-and-comment rulemaking. Secondly, an important factor supporting the requirement of notice-and-comment rulemaking in these cases, was the courts' concern with the substantial effect that a change in interpretation would have on the regulated industry -- a concern that is present in this case as well.[24/]

As discussed above, affected companies have relied on the Agency's historical interpretation of "primary mode of action" in the development of not simply their products, but their entire businesses. Consequently, administrative law principles mandate that any proposed change in interpretation undergo formal notice-and-comment rulemaking. These issues are simply too large not to be debated fully and fairly on the record.

III. A Jurisdictional Shift of Structural Cellular Wound Repair Products Is Inappropriate Under the Statutory Definition of "Biological Product," and Related Licensure Authority

During our testimony at the June 24 public hearing, AdvaMed also expressed concern that the contemplated jurisdictional shift would have statutory constraints under the definition of "biological product" and related requirements. Unlike the more fluid definitions of "device" and "drug," which are fashioned primarily around intended use and, thus, have been able to expand to address evolving technology, the definition of "biological product" was crafted more specifically and statically to include only those substances listed in the definition -- viruses, therapeutic serums, toxins, antitoxins, blood, blood components or derivatives,

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22/ Shell Offshore Inc. v. Babbitt, 238 F.3d 622, 630 (5th Cir. 2001).

23/ See Alaska Professional Hunters Association v. Federal Aviation Administration, 177 F.3d 1030, 1034-1035 (D.C. Cir. 1999); Shell Offshore Inc. v. Babbitt, 238 F.3d 622, 630 (5th Cir. 2001). Alaska Professional Hunters involved reliance of Alaskan guide pilots on verbal advice given by the FAA's Alaska Region over a number of years that certain regulations dealing with commercial pilots did not govern the guide pilots.

24/ See Shell Offshore Inc. v. Babbitt, 238 F.3d 622, 630 (5th Cir. 2001) (noting that the departure from the Department's long practice "substantially affected the regulated industry"); National Family Planning and Reproductive Health Association v. Sullivan, 979 F.2d 227 (D.C. Cir. 1992) (concluding that an agency action is a "substantive rule," if it does not merely interpret a regulation, but "produces ... significant effects on private interests").

allergenic products, and analogous products.[25/] This finite list of substances does not include structural cellular wound repair products, and the legislative history of the Public Health Service Act, as well as case law, further support that structural cellular and tissue products do not meet the definition of a "biological product," subject to licensure requirements.[26/]

A. Structural Cellular Wound Repair Products Are Not Any of the Listed "Biological Product" Substances

Structural cellular wound repair products do not meet the regulatory definition of any substance included within the scope of "biological product." By the express terms of the various biological substance definitions, they are not a virus,[27/] not a therapeutic serum,[28/] not a toxin,[29/] not an antitoxin,[30/] not a vaccine,[31/] not a blood or blood product,[32/] and not an allergenic product.[33/]

25/ A "biological product" is a "virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings." Section 262(i) of the Public Health Service Act, 42 U.S.C. § 351(i).

26/ Biologics license requirements are applicable to "biological products," as defined in the Public Health Service Act. Section 351(a) of the Public Health Service Act, 42 U.S.C. § 262(a).

27/ A virus is a "product containing the minute living cause of an infectious disease and includes but is not limited to filterable viruses, bacteria, rickettsia, fungi, and protozoa." 21 C.F.R. § 600.3(h)(1).

28/ A therapeutic serum is a "product obtained from blood by removing the clot or clot components and the blood cells." 21 C.F.R. § 600.3(h)(2).

29/ A toxin is a "product containing a soluble substance poisonous to laboratory animals or to man in doses of 1 milliliter or less ... of the product, and having the property, following the injection of non-fatal doses into an animal, of causing to be produced therein another soluble substance which specifically neutralizes the poisonous substance and which is demonstrable in the serum of the animal thus immunized." 21 C.F.R. § 600.3(h)(3).

30/ An antitoxin is a "product containing the soluble substance in serum or other body fluid of an immunized animal which specifically neutralizes the toxin against which the animal is immune." 21 C.F.R. § 600.3(h)(4).

31/ A vaccine is defined in FDA guidance as "an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration or therapy of any disease or infection." See FDA, Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (Jan. 1999).

32/ Blood and blood product means a product that "consists of human whole blood, plasma, or serum, or any product derived from human whole blood, plasma, or serum." 21 C.F.R. § 607.3.

33/ An allergenic product is a product that is "administered to man for the diagnosis, prevention or treatment of allergies." 21 C.F.R. § 680.1(a).

B. Structural Cellular Wound Repair Products Are Not "Analogous Products"

Besides the specified substances, the biological definition also includes "analogous product" within its terms, but it is clear from the regulations and case law, that an "analogous product" must have a strong "relation of likeness"[34/] to one of the specified substances. The regulations that have issued interpreting "analogous products" provide the following qualifying criteria:

- for products analogous to a virus, the product must be "prepared from or with a virus or agent actually or potentially infectious;"
- for products analogous to a therapeutic serum, the product must be "composed of whole blood or plasma or containing some organic constituent or product other than a hormone or amino acid, derived from whole blood, plasma, or serum;" and
- for products analogous to a toxin or antitoxin, the product must be "intended ... for the prevention, treatment, or cure of disease or injuries of man through a specific immune process."[35/]

Applying this framework, structural cellular wound repair products are not prepared from or with, and are not composed of, in whole or part, any of the listed substances. Structural cellular wound repair products also are not intended to prevent or treat disease or injury through a specific immune process.[36/] Cellular wound repair products, thus, are not "analogous" to a virus, therapeutic serum, or toxin or antitoxin, respectively.

Similarly, although the FDA has not yet formally defined products analogous to every substance in the statutory definition of "biological product," based on prior interpretations of the term "analogous," structural cellular wound repair products also do not qualify as analogous to vaccines, blood, blood components or derivatives, or allergenic products. They are not prepared from or composed of these substances, nor do they have the same function as any of these substances. As relevant case law guides us, structural cellular wound repair products simply cannot be said to have any "relation of likeness" with the substance listed in the definition of "biological product," by reason of "resemblance . . . of two or more

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34/ See Blank v. United States, 400 F.2d 302 (5th Cir. 1968) (applying the dictionary definition of "analogous" in determining whether a substance is analogous to a listed " biological product" substance).

35/ 21 C.F.R. § 600.3(h)(5)(i)-(iii).

36/ Where product definitions look to the intended function of the product, such as the definition of toxin and antitoxin, cellular wound repair products do not in any respect have intended uses analogous to these substances. Cellular wound repair products serve a structural, restorative function, not involving any specific immune process. See United States v. Loran Medical Systems, 25 F. Supp. 2d 1082 (C.D. Cal. 1997).

attributes, circumstances or effects."[37] The last time the Agency had this type of concern with "relation of likeness," a legislative amendment was deemed necessary.[38]

C. FDA's Cellular and Tissue Product Rulemaking Recognizes That Structural Cellular Wound Repair Products Are Not Subject To Licensure

As further evidence that there are statutory constraints in imposing the "biological definition" and related licensure requirements on structural cellular wound repair products, the Agency should consider its recent efforts to establish a cellular and tissue regulatory framework. In apparent recognition of the historical limitations of the "biological product" definition,[39] FDA promulgated regulations establishing a framework for cellular and tissue products pursuant to its authority to prevent disease transmission under Section 361 of the Public Health Service Act.[40] Importantly, the framework was not established pursuant to FDA's authority to review and approve biological products under Section 351 of this Act.[41] This separate regulatory framework for cellular and tissue products, in our view, is yet another indication that Section 351 has important limitations, and that any approval/license requirements would apply only to the extent that structural cellular products otherwise meet the existing statutory definitions of drug, device, or biological product.

37/ Blank v. United States, 400 F.2d 302 (5th Cir. 1968). In this case, decided prior to the inclusion of blood and blood components and derivatives within the scope of "biological product," the court relied on the dictionary definition of "analogous," in holding that blood is not analogous to therapeutic serum. Although this decision conflicted with an earlier decision (United States v. Steinschreiber, 219 F. Supp 373 (S.D.N.Y.), aff'd, 326 F.2d 759 (2d Cir. 1963) cert. denied, 376 U.S. 962 (1964)), there was sufficient concern regarding the FDA's authority that an amendment to the statute identifying blood and blood components and derivatives as biologicals, was sought and obtained. See Pub. L. No. 91-515, 84 Stat. 1297, 1308 (1970).

38/ Id.

39/ The list of substances subject to biologics licensure authority was last amended in 1970, when vaccines, blood, blood components or derivatives, and allergenic products were added. A formal definition of "biological product," including these substances, was enacted in 1997. Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 123(d).

40/ 42 U.S.C. § 264.

41/ 42 U.S.C. § 262. See 66 Fed. Reg. 5447 (Jan. 19, 2001); 66 Fed. Reg. 1508 (Jan. 8, 2000); 64 Fed. Reg. 52696 (Sept. 30, 1999). Prior regulations establishing requirements for tissue products also were promulgated pursuant to FDA's authority under Section 361 of the Public Health Service Act. See 62 Fed. Reg. 40429 (July 29, 1997).

Consistent with this cellular framework, the Agency historically has made a very legitimate case, that structural cellular wound repair products (and, for that matter, extracellular, bone repair, and a wide variety of other tissue and cellular-derived products), are devices[42/] subject to device premarket review authority.[43/] However, the Agency has not, and we believe cannot, make a similar case for biological licensure authority and related requirements for this class of products.

AdvaMed and its members also strongly support proposed and final regulations establishing registration, donor screening, and Good Tissue Practice requirements pursuant to Section 361 of the Public Health Service Act. These requirements are important measures to further assure the safety of cellular and tissue products. However, the Agency cannot impute biologics license requirements to structural cellular wound repair products, based on this Section 361 authority. "Biological" definitional constraints, thus, must be considered by the Agency as part of the jurisdictional decisionmaking for this category of products.

IV. Jurisdictional and Operational Considerations for Structural Cellular Wound Repair Products

As stated above, where the primary mode of action of a cellular wound repair product is a structural/repair/replacement function, the definition of device, as well as FDA guidance documents, provide that the product is a device to be regulated by CDRH under device premarket authorities. Further, just as structural cellular wound repair products should not be regulated by CBER under biological product authorities, they also should not be reviewed by CBER under device authorities. Although CBER currently regulates single entity products such as in vitro diagnostic devices used in blood banking and certain other devices under device authorities, combination products have greater jurisdictional constraints than these

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42/ A "device" is defined as an "instrument, apparatus, implement . . . implant, . . . or other similar or related article . . . , which is . . . intended to affect the structure or any function of the body of man . . . and which does not achieve its primary intended purposes through chemical action within or on the body of man . . . and which is not dependent upon being metabolized for the achievement of its primary intended purposes." Section 201(h) of the FFDCA, 21 U.S.C. § 321(h).

43/ See FDA, Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991) ("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"); FDA, Intercenter Agreement between the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health (Oct. 31, 1991) ("cultured skin will be regulated by CDRH under the Medical Device Authorities"); FDA, Proposed Approach to Regulation of Cellular and Tissue-Based Products (Feb. 28, 1997) ("[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, by means other than metabolic or systemic action, are regulated as devices by CDRH"). See also Attachment 2.

products. In contrast to single entity products, Section 503(g) of the FFDCA[44/] and 21 C.F.R. Part 3, which apply to combination products, must be considered. These authorities unambiguously instruct that, "[w]here the primary mode of action is that of . . . a device, the persons charged with premarket review of devices shall have primary jurisdiction."[45/] Pending legislation, H.R. 3580, supported by AdvaMed's members, reaffirms this approach.[46/]

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 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. Consequently, for these products, innovative solutions to permit continued use of device authorities is essential.

V. There Are No Public Health or Other Compelling Reasons Supporting a Shift in Jurisdiction of These Products

There are two provisions of law that address the concept of jurisdictional transfer: the transfer of a product "classification" and/or a review Center under Section 563 of the FFDCA, and the transfer of a review Center under 503(g) of the FFDCA and implementing regulations.[47/] Section 503(g) and its implementing regulation apply to combination products, and Section 563 applies to drugs, biological products, devices, and combination products. Although Section 503(g) and Section 563 authorities articulate a slightly different decisionmaking standard, both instruct the Agency that, unless the sponsor consents to the transfer, a high evidentiary standard is needed to justify a proposed shift in jurisdiction.

44/ 21 U.S.C. § 353(g).

45/ Section 503(g) of the FFDCA, 21 U.S.C. § 353(g); 21 C.F.R. § 3.4.

46/ That legislation would confirm by statute that products which meet the definition of device or drug or biological product, shall be regulated only by the FDA personnel who are primarily charged with regulation of that category of product.

47/ See Sections 503(g) and 563 of the FFDCA, 21 U.S.C. §§ 360bbb-2, 353(g); 21 C.F.R. § 3.9(b).

Section 563 of the FFDCA provides that, when a request has been submitted concerning the classification of a product or FDA Center, unless the sponsor otherwise consents, the Agency may not modify its decision except "for public health reasons based on scientific evidence."[48/] Thus, under this provision, the Agency may not simply offer up a theoretical public health reason, but must provide actual scientific evidence that a public health concern in fact exists, such that a transfer is justified.

Under Section 503(g) of the FFDCA relating to combination products, which in turn has been implemented pursuant to Part 3 of the regulations, there is a similar evidentiary standard imposed for shifts in jurisdiction. Specifically, Part 3 regulations state that a formally "designated agency component" may not be changed without the written consent of the sponsor, unless it is "to protect the public health or for other compelling reasons."[49/] Accordingly, by the black letter of this standard, the Agency is instructed that: (1) a public health reason, if offered, must be for purposes of protection (i.e., there must be a concern to protect); and (2) the public health or other reason must be found to be "compelling."

In implementing these provisions, Congress emphasized the importance of binding jurisdictional decisions,[50/] once they have been made and relied on by sponsors. The imposition of a very high evidentiary standard, absent sponsor consent, is a clear congressional signal that sponsors should be protected in instances where public health or other compelling reasons have not been established.

Consequently, in this case, where companies have relied on jurisdictional decisions -- in some cases for over a decade -- to build their product franchises and businesses, Congress would surely have concerns if protection of public health or other important reasons were not demonstrated and discussed through notice and comment, prior to the jurisdictional change. CDRH jurisdiction for structural tissue-engineered products has been so entrenched and longstanding, that Congress would be certain to demand compelling rationales for any proposal of change, regardless of how jurisdictional decisions for these products were first made.[51/]

Thus far, the FDA has not formally put forward any specific, supported public health concerns or other compelling basis for the proposed shift in jurisdiction. Indeed, in the May 15 Federal Register notice, and during the subsequent June 24 public meeting, no rationale at

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48/ Section 563 of the FFDCA, 21 U.S.C. § 360bbb-2.

49/ 21 C.F.R. § 3.9(b).

50/ See H.R. Rep. No. 105-43, at 27 (1997) (the "designation shall be final and binding").

51/ Section 503(g) and its implementing regulations at Part 3 provide that the FDA will designate the Center with review responsibility for a combination product, in response to a request. Section 563 broadens this authority to include products other than combination products, and provides that, in response to a request from a person who submits an application, petition, notification or other request, concerning the classification of a product as a drug, biological product, device, or combination product, or the Center that will review the product, the FDA will identify the classification and/or reviewing Center. Section 563 also codifies the requirement that responses must be provided within 60 days.

all was provided. The Agency did, however, request industry to speak to public health issues, and, during their presentations at the June 24 meeting, manufacturers of tissue-engineered devices uniformly stated that neither clinical testing nor marketing of these products over the last several years had revealed any public health concerns. The evidence they relied on in making these statements included: (1) extensive preclinical and postmarket safety experience involving tens of thousands of products distributed worldwide; (2) the extensive and rigorous premarket review and approval process for these products; and (3) the review experience and expertise of CDRH personnel that participated in the premarket reviews. Based on this data and information, there is no public health reason, compelling or otherwise, to justify a jurisdictional transfer.

Regardless of how jurisdictional decisions for this class of product were initially made, Congress has been unambiguous on the need for FDA to establish a high evidentiary standard before altering a company's jurisdictional pathway, particularly one that has been relied on for so long and so extensively by industry. We trust that the Agency will heed this standard as it proceeds to make decisions for structural cellular wound repair products.

VI. Executive Order 12866 and the Regulatory Flexibility Act Require That FDA Consider the Costs and Benefits of This Proposal Prior to Its Adoption and Implementation

In 1993, the Administration issued Executive Order 12866 intended to reform the regulatory process. One of the defining principles of this Executive Order was that, for each significant regulatory action,[52/] federal agencies should be directed to evaluate and weigh all costs and benefits of alternative regulatory approaches, and to "select those approaches that maximize net benefits (including potential economic, public health and safety, and other advantages; distributive impacts; and equity)."[53/] The principal reason for this Order was to avoid significant regulatory actions that are poorly articulated and rationalized from a cost-benefit perspective. The current Administration takes this Executive Order seriously and has delayed and/or reformed significant regulatory actions that have not been consistent with the themes of the Order.[54/] Similarly, the Administration considers important the impact of regulatory actions on small businesses.[55/] AdvaMed is concerned with the adverse affects that this effort will have on small businesses, which represent the predominant share of this industry. AdvaMed also is concerned that the costs and benefits of the Agency's

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52/ Executive Order 12866 defines significant regulatory actions as "any substantive action by an Agency" that is likely to result in a rule. For a discussion of why new regulatory authority is needed to accomplish the Agency objectives, see Section II above.

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

54/ For example, because of concerns that federal privacy regulations promulgated pursuant to the Health Insurance Portability and Accountability Act ("HIPAA") did not take into account certain public health considerations, Secretary Thompson delayed their issuance and directed the Department of Health and Human Resources to propose appropriate modifications to address those concerns. See 67 Fed. Reg. 14776, 14777 (Mar. 27, 2002).

55/ See Regulatory Flexibility Act, 5 U.S.C. §§ 601-612.

jurisdictional proposal have neither been adequately articulated nor considered,[56/] and that, once considered, costs will significantly outweigh any perceived advantages.

As the Agency heard repeatedly during the Part 15 hearing, CDRH has established very capable expertise, and significant invested knowledge in both the technology and the clinical disciplines applicable to this technology. CDRH now has a decade or more of experience with structural tissue-engineered products. Further, as noted above, the products under consideration have been marketed without any public health concerns for a number of years. Accordingly, any potential benefits, required to be identified by Executive Order 12866, remain unclear.

By contrast, the costs of the proposed jurisdictional shift are quite real and significant to manufacturers of tissue-engineered products. As noted above, regulation of tissue-engineered products by CBER would have an enormous economic and logistical impact on these manufacturers. They would be required to invest substantial funds into the development and implementation of new regulatory systems for biological products. In addition, product development and related business plans would need to be substantially revised and replaced, and new personnel and training programs would need to be added.

Given the lack of any compelling public health or other benefit presented by a shift in jurisdiction, and the significant economic and logistical burden on manufacturers, AdvaMed believes that the directive under Executive Order 12866 to "select ... approaches that maximize net benefits," has not been, and cannot be, met. We, therefore, request that the Agency give serious consideration to, and articulate its position on, costs and benefits under this Order, so that the public may fully understand and debate these issues.

VII. Conclusion

As stated by AdvaMed and its members at the June 24 hearing, and reiterated in this correspondence, manufacturers of tissue-engineered products have relied on historical device jurisdiction to, among other things: develop and establish product development strategies and testing programs; develop quality systems and postmarket compliance plans; hire personnel; and structure their market approaches. In short, all aspects of their businesses have been created and sustained based on the device paradigm. A shift in jurisdiction of the products at issue, thus, will have significant financial, logistical, organizational, and personnel impacts on these companies and their future -- of grave concern to the industry, since there already exists a very fragile environment for this area of scientific innovation.

Industry has had a long and entrenched reliance on CDRH jurisdiction, as a result of FDA's long and entrenched historical interpretation of primary mode of action based on primary intended function of the combination product. We, therefore, urge, under both legal and equitable principles, that jurisdiction for these products be left intact at CDRH.

56/ The benefits of shifting jurisdiction from CDRH were not articulated by the Agency in its May 15, 2002 Federal Register notice or during the June 24, 2002 Part 15 hearing.

We appreciate your full consideration of our concerns and look forward to the opportunity to meet directly with you on this issue, which is so vitally important to so many of our members. We will telephone your office in several weeks to begin the process of scheduling a meeting date.

Sincerely,

Janet Trunzo
Vice President
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