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HAND DELIVERED

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 02N-0169

To Whom It May Concern:

We are submitting the attached comment to the above-referenced docket in response to FDA's *Federal Register* Notice on the regulation of combination products containing live cellular components, in particular, combination products for wound healing that consist of autologous or allogeneic living human cells combined with a device matrix. *67 Fed. Reg.* 34,722 (May 15, 2002). We look forward to the agency's response.

Sincerely,



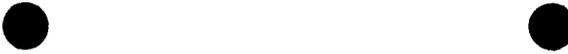
by Melissa Moonan

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Hale and Dorr, LLP

02N-0169

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**COOK GROUP, INC.'S COMMENT ON JURISDICTIONAL CLASSIFICATION,
ASSIGNMENT, AND PREMARKET REVIEW OF COMBINATION PRODUCTS
THAT CONSIST OF LIVING HUMAN CELLS IN COMBINATION WITH A
DEVICE MATRIX**

FDA Docket No. 02N-0169

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Washington, D.C. 20004**

Cook Group, Inc. (“Cook”) submits this comment in response to a *Federal Register* Notice on jurisdictional classification, assignment, and premarket review of combination products that consist of living human cells in combination with a device matrix, in particular, products that consist of autologous or allogeneic living human cells combined with a device matrix for wound healing. *See* 67 Fed. Reg. 34,722 (May 15, 2002) (“May *Federal Register* Notice”). While we appreciate the opportunity to comment, it is Cook’s belief that, to a large extent, the agency’s approach to such products is determined by statute. The agency’s approach must conform to the requirement that FDA assign jurisdiction based on the primary mode of action.

Specifically, interpreted in concert with the product definitions in the Federal Food, Drug, and Cosmetic Act (“FDC Act”), the requirement that combination products be regulated according to their primary mode of action means that combination products that meet the definition of a device when considered as a single entity should be regulated as a device, and the same basic rule holds true for products that meet the definition of a drug or a biologic. The same legislation that enacted the primary mode of action requirement for combination products also amended the definitions of “device” and “drug” to make clear that these articles could encompass products that operate primarily like a device, though enhanced by a drug component, or primarily as a drug, though enhanced by a device component. This means that wound healing products with cellular components that meet the definition of a device should be regulated as devices.

For device/biological product combinations that do not clearly meet one definition to the exclusion of the other, the law assigns jurisdiction to CDRH. Only in the rare instances where the identity of the product cannot be determined, two approvals may be necessary. In these rare cases, the agency should rely on reasonable considerations to permit both approvals to occur in a single center. For example, because CDRH currently has jurisdiction over these wound healing products, maintaining CDRH’s authority will promote continuity, efficiency and review quality, thus protecting the public health by ensuring that the review and clearance or approval of important products are well done and not needlessly delayed. Further, CDRH has the regulatory authorities and experience to protect the public from risks associated with cell-based products. In particular, validation requirements and design and other manufacturing controls contained in the Quality System Regulation apply as readily to the processing of cell-based products as they do to mechanical processes, and provide adequate assurances of safety and effectiveness for these products.

Although the agency has specifically solicited comments on wound dressings with live cellular components, Cook stresses the importance of developing a coherent policy for all combination products. The approach advocated in this comment is a basis for such a policy because the approach relies on the statutory provisions that apply to all combination products. Cook believes the degree of uncertainty that currently exists concerning the regulation of combination products and the impact of any decision the agency reaches argue in favor of implementing the interpretation advocated in this

comment by the rulemaking procedures of section 553 of the Administrative Procedure Act. Such procedures are necessary for any policy that exceeds a mere interpretation of statutory language, but as a matter of law, will be insufficient to legitimate a policy that does not rationally interpret or implement “primary mode of action” or other parts of the Act.

I. JURISDICTIONAL APPROACH TO COMBINATION PRODUCTS

The agency’s approach to regulating products related to wound healing, and combination products¹ in general, has created uncertainty and possibly chilled innovation. The objective of the agency in considering responses to the three questions posed in the May *Federal Register* Notice should be the development of a regulatory approach that is supported by the statute, workable, and will yield reasonably predictable results. Further, the agency should develop an approach to wound healing products that is mindful of all combination products because all such products are subject to the same statutory authority and a piecemeal approach will undermine the law’s purpose of facilitating prompt and predictable review responsibilities. The agency should also consider single entity products that are potentially subject to premarket review considerations by more than one Center in developing its approach, because such products raise similar assignment issues and are also subject to potentially protracted jurisdictional determinations.

A. Determining Primary Mode of Action

1. *Primary Mode of Action Must be Analyzed with Reference to the Definition of Device.* Section 503(g) of the FDC Act² requires FDA to determine the “primary mode of action” of a combination product—or whether the combination product acts primarily as a drug, device, or biological product—and to assign premarket review jurisdiction accordingly. An application of this provision to wound dressings with live cellular components requires an understanding of the definitions of devices and biological products.

Section 201(h) of the FDC Act defines “device” as:

¹ FDA has defined the term “combination product” at 21 C.F.R. § 3.1(e) to include products that combine components of two or more FDA-regulated products; products that combine two or more complete FDA-regulated product types; FDA-regulated products intended for use only with another FDA-regulated product; and certain investigational combinations.

² Section 503(g) provides in relevant part:

(1) The Secretary shall designate a component of the [FDA] to regulate products that constitute a combination of a drug, device, or biological product. The Secretary shall determine the primary mode of action of the combination product. If the Secretary determines that the primary mode of action is that of . . .

(A) a drug (other than a biological product), the persons charged with premarket review of drugs shall have primary jurisdiction, or

(B) a device, the persons charged with premarket review of devices shall have primary jurisdiction, or

(C) a biological product, the persons charged with premarket review of biological products shall have primary jurisdiction.

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is –

- (1) recognized in the National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or in other animals, or
- (3) intended to affect the structure or function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent on being metabolized for the achievement of its primary intended purposes.

The final clause of the definition provides a means for distinguishing devices from other FDA-regulated products. Devices do not achieve their “primary intended purposes” through drug-like action, *i.e.*, through chemical or metabolic action in or on the body. In other words, a product may be a device even if it includes a drug component that acts in or on the body if the drug action is secondary to the device effect. The Safe Medical Devices Act of 1990 (“SMDA”) substituted the words “its primary” for the phrase “any of its principal” in paragraph (3) of the definition to ensure a clear understanding that secondary drug effects do not void a product’s device status. Additionally, this change, and a change to the drug definition³, were made to ensure that the jurisdictional bases for regulation and the internal review assignment mechanism set forth in section 503(g) were consistent.

Section 351 of the Public Health Service Act (“PHS Act”) provides for the regulation of biological products, and applies to:

any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound) applicable to the prevention, treatment, or cure of diseases or injuries of man.

Thus, biological products, unlike devices, are limited by statute to certain specifically defined entities. In practice, most biological products are regulated as drugs because they function by chemical or metabolic means or, in rare cases, as devices because they are devices, *e.g.*, an in vitro diagnostic, or are components of devices.

When a biological product is combined with a device, however, as is the case with wound dressings containing live cellular components, section 503(g) requires the agency to determine whether or not the primary mode of action of the product is a metabolic or chemical effect produced by the biological component. If not, then the product is a

³ Congress amended section 201(g)(1)(D) to permit application of the term “drug” to combination products with drug and device components. Specifically, the SMDA struck language providing the term “drug” does “not include devices or their components, parts, or accessories.”

device within the jurisdiction of CDRH. Congress enacted this provision to address dissatisfaction within regulated industry over FDA's approach to regulating combination products and intended this provision to establish "firm ground rules" to ensure consistent, predictable treatment of combination products. *See* S. Rept. No. 101-513, 30 (Oct. 9, 1990). Implicit in Congress's desire for consistency was the intention to create a rule that would yield predictable results when applied to emerging technologies that do not fit neatly into the conventional categories of drug, device, and biological product. *See id.* (discussing the range of new multi-center products).

2. **The Identity of a Combination Product is Dependent on How It Achieves its "Primary Intended Purposes."** Neither Congress nor FDA has defined "primary mode of action" explicitly. In the May *Federal Register* Notice, however, FDA suggested that analyzing a product's primary mode of action requires "clear scientific data" to "identify how the product acts on the body and to determine the relative contribution of each of its component parts." This analysis, when applied to device/biologic combinations, invites a determination of a product's activity at the cellular level, and, we believe, fails to follow the legislative direction of Congress, ignoring how the "primary intended purposes" of a product are achieved. *See* § 201(h) of the FDC Act.

Indeed, the statute requires taking another approach to determining the primary mode of action of any particular combination product. Even without an explicit definition of "primary mode of action," Congress intended its meaning to be understood by reading section 503(g) with the conforming amendments made to the definitions of "drug" and "device" in the SMDA, the legislation that first addressed combination products. *See United States Nat'l Bank of Oregon v. Indep. Ins. Agents of Am., Inc.*, 113 S. Ct. 2173, 2182 (1993) (statutory provisions should be read in context of the entire statute). The definitional changes make clear that the terms "drug" and "device" encompass products that act on the body in more than one way, but for the most part, act through a drug or a device mechanism. In particular, the change to the definition of device means that a drug/device combination that does not achieve its primary intended purposes through chemical or metabolic action in or on the human body is legally a device and should be regulated accordingly. The same is true for device/biological product combinations.⁴ In other words, the determination of primary mode of action in the first instance does not necessarily involve an intricate comparison of a combination product's components, but does involve a determination of the product's legal jurisdictional status, *i.e.*, through an assessment of whether its primary intended purposes are achieved through chemical or metabolic action within or on the human body.

⁴ This view reflects the fact that biologics have a drug identity that should not be ignored when assessing FDC Act jurisdiction issues. To do so, would be to elevate the PHS Act authority over the FDA's major authorizing statute and the statute in which Congress chose to include the authority under section 503(g) to sort out the review placement of combination products, including those containing biologics. Indeed, section 351(j) of the PHS Act explicitly recognizes that biological products are subject to approval as new drugs, and exempts them from new drug approval if they have an approved biologics license. *See also* section 351(g) of the PHS Act (stating that the PHS Act does not modify, repeal, supersede, etc., the FDC Act).

Thus, the first, and often the definitive, step in determining the primary mode of action of a combination product is to evaluate the product's primary intended purpose. If it is a device purpose that is not primarily achieved through metabolic or chemical action in or on the body of man, then CDRH should regulate the product. Likewise, if a product's primary intended purpose is achieved through such chemical or metabolic action, the product could be regulated as a drug or biologic. Simply put, if the product meets the definition of one of the product types regulated by FDA, jurisdiction should be assigned to the Center with authority over that product type.⁵

This view is fully supported by FDA's *Federal Register* document announcing the agency's approach to implementing SMDA. There, the agency stated, "if a product is a combination of a drug and a device, and the drug functions to enhance the device effect, the product will be regulated as a device." 56 *Federal Register* 14111, 14112 (April 5, 1991). Thus, FDA understood section 503(g) to mean that products with non-device components would be regulated as devices, even if the non-device component produced a secondary metabolic or chemical effect that enhanced the achievement of the product's primary intended purpose.

Relying on the presence of cellular activity as the determinant of primary mode of action clearly clashes with the statute as written. While the metabolic action of a biological product may enhance the therapeutic effect of a device, at the cellular level, structural and metabolic activities may be so closely entwined that focusing on them can divert the agency from appreciating the product's primary intended purpose as a device. Most products that are the subject of this call for comments have a nonmetabolic component that encourages regeneration and healing, which is enhanced by a cellular component that promotes growth; the activity of the cellular component is in turn supported by the device component that provides a scaffold for growth and protects the wound. The relationship of the two components in achieving healing is likely to be clearer than the relationship of the two in achieving a cellular effect. In other words, by positing cellular activity as the basis to determine premarket review assignment, FDA has overlooked the jurisdictional identity of combination products, which is tied to the key regulatory concept of primary intended purpose. For wound dressings with cellular components, the primary intended purpose is generally the device purpose of providing a skin-like scaffold for the growth of new skin, a purpose that may be enhanced by additional migration and proliferation of cells due to the presence of live cells.

The TransCyte® product, marketed by Advanced Tissue Sciences, illustrates the assignment of jurisdiction according to primary intended purpose. This product consists

⁵ Although under the PHS Act, biological products are not defined by mode of action, sections 201(h) and section 503(g) of the FDC Act demonstrate that Congress viewed biologics, like drugs, as achieving their primary intended purposes through chemical or metabolic action within or on the body of man. See section 503(g)(1)(A) (stating that products with a primary mode of action of a drug will be regulated by CDER, unless they are biological products). See also note 4, *supra*. This means that device/biological products that achieve their primary intended purposes through chemical or metabolic action in or on the human body should be regulated by CBER. However, where the combination cannot be demonstrated to achieve its primary intended purposes through chemical or metabolic action, section 503(g) dictates that CDRH, not CBER, is the lead Center.

of a nylon mesh bandage-like component, a semi-permeable silicone barrier layer, porcine dermal collagen, and cultured human neonatal fibroblasts. The nylon mesh membrane serves as the scaffolding onto which the fibroblasts are grown. As the fibroblasts proliferate, they secrete dermal collagen, extra-cellular matrix proteins, and growth factors. Following freezing, no cellular activity remains; however, the tissue matrix and growth factors are left intact. In this instance, the main therapeutic action of the product is to protect an open wound to facilitate the body's natural healing processes, a purpose associated with conventional devices such as bandages. The growth factor interacts with the skin to minimize the development of scar tissue, a benefit that enhances the primary purpose of protecting a wound to induce healing. Thus, the primary intended purpose is not achieved by chemical or metabolic activity, and the product meets the device definition.

The addition of live cells does not alter this conclusion. For example, Advanced Tissue Sciences also markets Dermagraft®, a cryopreserved wound dressing that incorporates live human fibroblasts seeded onto a bioabsorbable polyglactin mesh scaffold. The fibroblasts proliferate to fill the interstices of the scaffold and secrete dermal collagen, matrix proteins, growth factors, and cytokines. The live cellular activity helps facilitate absorption of the dressing and wound healing, but the purpose of the product as a whole is primarily that of a bandage in that it supplies protection and replicates the structural function of skin. Like the TransCyte® product, Dermagraft® properly falls within the jurisdiction of CDRH.

B. Considerations Favoring CDRH Review of Wound Dressings with Cellular Components

In almost all instances, the analysis discussed above will yield rational product jurisdiction determinations. As products become more sophisticated and increasingly achieve their therapeutic ends by complicated structural and metabolic interactions, determining the primary mode of action may be, in certain instances, extremely difficult. In these rare instances where the statutory mandate does not yield clear results, more than one approval may be necessary for the same product. In keeping with the Congressional goal of streamlining the review of combination technology and encouraging innovation, the agency should, whenever possible, avoid requiring premarket reviews by multiple Centers for a single product.⁶ Rather, the agency should rely on other relevant considerations to determine the lead Center for these products.

1. There is a Statutory Preference for Jurisdiction in CDRH. As discussed in the previous section, the identity of the combination product determines the Center with jurisdiction over the product, so that CDRH has authority over device/biologic combination products that are devices within the meaning of the FDC Act and CBER has authority over such products when the product's primary intended purpose is achieved through metabolic or chemical means. Certain products, however, may meet both definitions, or may incorporate features of each so that meaningfully identifying a single

⁶ The concern is to avoid two independent regulatory clocks. Cook fully supports using consults as a means of ensuring full, quality reviews and lead jurisdiction in one Center.

identity for the product would be arbitrary. For such products, the FDC Act authority that defines the product as a device controls over the PHS Act authority that would define the product as a biological product.

Specifically, section 503(g) supports the conclusion that CDRH has jurisdiction over combinations that are both devices and biological products. While limiting CDER's jurisdiction to any combination products that constitute a drug "other than a biological product," the provision does not qualify the assignment of jurisdiction to CDRH over combination products that constitute devices. *See* FDC Act § 503(g)(1)(A), (B). The unqualified assignment of devices to CDRH, coupled with the limited assignment to CDER of only those drug combinations that do not constitute biological products, reveals a Congressional intent that devices that also constitute biological products must be regulated by CDRH. This conclusion is buttressed by section 351(g) of the PHS Act, which states:

Nothing in the chapter shall be construed as in any way affecting, modifying, repealing, or superseding the provisions of the [FDC Act].

Therefore, as a matter of law, even where a combination product is made up of mostly all biologic components, if it is a device because it does not achieve its primary intended purposes through chemical or metabolic action within or on the body of man, CDRH shall be assigned as the lead Center to review and approve the product.

2. **Historical Determinations Favor CDRH Jurisdiction.** The way the agency has regulated a combination product historically is another important criterion in determining how the agency should regulate similar combination products as they evolve. Although the primary mode of action analysis discussed in this comment will result in CDRH having jurisdiction over many wound dressings with live cellular components, for certain products, the determination may be unclear. Wound healing products that induce regeneration of dermal tissue may have both significant device and chemical or metabolic functions, thus a mixed primary intended purpose. As applied to such products, section 503(g) becomes ambiguous. Consistent with the Congressional goal of ensuring predictability and consistency, the agency should assign jurisdiction for such products to CDRH, the Center that historically has had jurisdiction over similar combination products. Of course, a CBER consult, or in rare cases, an approval under both the FDC and PHS Acts, would be entirely appropriate.

To do otherwise would result in a critical loss of expertise. CDRH has approved all combination interactive wound healing products to date and not only is the expert center with regard to their primary device function, but has gained the institutional experience and expertise required to effectively regulate these combination products by shepherding them through the steps in their technological development, including the addition of cellular components. To switch the products over to CBER at this time would be to waste years of CDRH's institutional knowledge and hands on experience with such devices.

3. **The Nature of the Device Industry Favors CDRH Jurisdiction.** The efficiencies realized by maintaining jurisdiction in CDRH, when the law does not require placement in CBER, are particularly important in light of certain aspects of the device industry and the marketing of medical devices. First, medical devices have a more rapid development cycle and shorter life cycle than biological products. The survival of medical device companies is dependent on their ability to innovate and update their products incrementally, and achieve market entry quickly. This is a much different paradigm from the one typical of biological products, which have slower development paths and longer product lives. Because of the constant iterations in device product development, a predictable, efficient, and responsive regulatory process is key. CDRH knows the products, and device and tissue engineering firms have planned for and invested in device regulatory controls and pathways to market. Switching the regulatory regime for wound healing products or any other devices from CDRH merely because a product has advanced technologically turns the expectations of device manufacturers on their head without a public health benefit or other justification.

Second, the fledgling state of the tissue engineering industry and the small size of most medical device companies magnifies the impact of regulatory disruptions for companies that have invested their resources in developing state of the art medical devices, clinical programs, and device production facilities, and in educating CDRH about their products. Such a change must be legally based how the product achieves its primary intended purposes, *i.e.*, its primary intended purpose is achieved through chemical or metabolic action. Where the appropriate legal jurisdiction cannot be determined by the combination's identity, ordinarily jurisdiction should remain in CDRH.

4. **CDRH's Regulatory Authorities and Approach Assure Safe and Effective Combination Products.** The CDRH External Review subcommittee of FDA's Science Board concluded in its report, *Science at Work in CDRH: A Report on the Role of Science in the Regulatory Process* (Nov. 16, 2001) ("Report to FDA's Science Board"), that however combination products are regulated (*i.e.*, as a drug, biologic, or device), they "need to be regulated with an approach that embodies the philosophy of CDRH, one that is least burdensome, predictable, timely, transparent, interactive, and effective." *See id.* at page 18 of 24; *see also* Recommendation 12 of the Report to FDA's Science Board (reiterating that regulation of combination products "requires an approach that is least burdensome and embodies the philosophy of CDRH"). We agree with the Report's conclusion that premarket review by CDRH with least burdensome data requirements is the optimal way to review combination products, especially products that have been regulated as devices in all their previous iterations. Nonetheless, whether previously regulated as a device or not, if a combination product meets the definition of a device, it should be regulated as such.

Importantly, CDRH has broad experience in regulating combination products. For example, the Office of Device Evaluation's Annual Report for Fiscal Year 2000 notes that CDRH was asked to review 21 of the 23 Requests for Designation ("RFDs") made that year, and that of the 16 RFDs completed that year, 10 products were assigned to CDRH for review (1 was withdrawn and the other 5 went to CDER or CBER).

Moreover, and also importantly, CDRH has the expertise, not just from experience, but also from active research on scientific issues concerning such products. The CDRH Office of Science and Technology's ("OST's") Fiscal Year 2001 Annual Report ("OST 2001 Annual Report") lists a number of research and testing programs in the physical, life, and engineering sciences that provide CDRH reviewers with specific scientific expertise for product review and health risk analyses. Significantly, OST is conducting research projects specifically related to tissue engineering.⁷

For complex combination products, the PMA process provides the flexibility and interactive opportunities (pre-IDE, pre-PMA and 100 day meetings) necessary to design a clinical development program that will provide the data necessary to thoroughly understand and approve devices that incorporate live cells. Further, the availability of the Humanitarian Device Exemption ("HDE") pathway to market, which has no analog in biologics regulation, and with which CDRH has far more experience than CBER,⁸ has resulted in interactive wound healing products becoming available to patients for whom no available therapies have worked. The importance of the HDE program in bringing innovative products to market should not be compromised by denying access to it for devices that incorporate live cells. Moreover, such a change would be unsupported by the law. Under section 503(g) of the FDC Act, FDA has no discretion to assign a combination product with a device primary mode of action to CBER for review, or, of course, to move a combination product device from CDRH to CBER.

Manufacturing is another important aspect of safety and effectiveness of devices and biologics, and the capability of a manufacturing process to produce safe, pure, and potent biologics has been an emphasis in the biologics regulatory scheme. However, good manufacturing practices ("GMPs") for drugs, which apply to biologics do not provide any advantage over the device Quality System Regulation ("QSR") in 21 C.F.R. Part 820 in achieving quality and consistency for combination device-biologic products. The QSR provides a flexible framework for the manufacture of combination products that emphasizes design and process controls and validation. Further, the device GMPs require manufacturers to write procedures to "fill in the details that are appropriate to a given device according to the current state of the art manufacturing for that specific device." 61 *Fed. Reg.* 52602, 52,603 (Oct. 7, 1996). Indeed, at the June 24, 2002 public hearing held by FDA ("public hearing"), Sally Seaver, the Chair of the United States Pharmacopeia's ("USP's") Expert Committee on Gene Therapy, Cell Therapy and Tissue Engineering, stated that the QSR was an "extremely helpful" approach, as well as a "more comprehensive approach to quality than CBER's specification for the quality function." Ms. Seaver stated that the USP found the QSR's requirements for design controls and

⁷ For example, under the subheading of tissue engineering under the heading of "Host Response" in the 2001 Annual Report, OST reports its development of cell adhesion assays to determine the ability of cells that are cultured/grown on polymer or natural substrates to adhere and maintain their cell phenotype and other characteristics. The project has resulted in the Tissue Engineered Medical Products Division of the American Society for Testing and Materials ("ASTM") forming a task force to develop an ASTM standard for cell adhesion assays for tissue engineering. A draft ASTM standard for characterizing Type I collagen also resulted from OST's work in tissue engineering standards. Also under the heading of Host Response, a number of research products are listed that address the interaction of biomaterials and human tissues.

⁸ We found no approved HDEs listed on CBER's device approvals web page.

risk assessment particularly important to the development of manufacturing processes that will produce safe cell therapy products that will consistently act as expected. Indeed, pre-production design controls are critical to the intrinsic safety and effectiveness of medical devices, and thus to combination device and cellular products. Not only do drug GMPs not include design controls, CBER investigators, while familiar with design controls through CBER's regulation of blood bank software and certain *ex vivo* blood banking and biologic processing devices, do not have CDRH's in-depth knowledge and experience with the implementation and auditing of design controls, particularly for implantable devices, which are the devices most likely to incorporate live cells in the future.⁹

The concerns raised by certain public hearing participants regarding product safety are all subject to requirements under Part 820. State of the art specific requirements for cellular components are required to be part of written procedures for manufacturers of devices that incorporate cells as components. For example, procedures for sourcing, identifying, tracking, and recordkeeping for cellular components are required by QSR purchasing and acceptance, identification and traceability, and device history requirements, as well as being part of design and process controls and validation. QSR requirements likewise cover other GMP requirements specific to drugs and biologics under Part 211, such as component in process and final product testing, stability testing, container and closure inspection and testing, and microbiological contamination prevention. Indeed, the comprehensiveness of Part 820 is demonstrated by the fact that the proposed rules on donor suitability and good tissue practices under Part 1271 for devices that incorporate human cellular or tissue components are intended to supplement, not supersede Part 820. The proposed requirements will further codify and add specificity for donor screening and recordkeeping responsibilities already required by Part 820 to be established through state of the art procedures rather than adding new types of controls to the device manufacturing process.

New issues that arise with regard to data requirements and clearance or approval, manufacturing, or with any other aspect of product development and marketing can be addressed in guidance, and, where necessary, through consultation with other Centers. A multicenter guidance, *Chronic Cutaneous Ulcer and Burn Wounds--Developing Products for Treatment* (June 2000) on wound healing products already exists, as does a CDRH draft guidance on IDE submissions, *Guidance for the Preparation of IDE Submissions for an Interactive Wound and Burn Dressing* (April 1995). In addition, the combination product regulations contemplate that the lead Center may consult with the Center with experience with the secondary product component. See 21 C.F.R. § 3.4(b). In fact, FDA Ombudsman's Office just issued a standard operating procedure and policy ("SOPP") entitled *InterCenter Consultative/Collaborative Review Process* (July 2002), which is

⁹ Indeed, implantable stents are an example of the evolution of such devices. Significantly, the FDA Ombudsman determined pursuant to section 503(g) of the FDC Act that cardiovascular stents that incorporate a drug coating have a primary mode of action of a device because the drug's role is secondary to the uncoated stent, which functions physically to maintain lumen patency, whereas the coating augments the safety and/or effectiveness of the uncoated stent by minimizing restenosis. See *Jurisdictional Update: Drug Eluting Cardiovascular Stents*, FDA Office of the Ombudsman (www.fda.gov/oc/ombudsman/stents.html).

specifically intended “to improve intercenter communication on combination products, as well as the timeliness and consistency of intercenter consultative and collaborative reviews.” Among other things, the SOPP calls for adherence to due dates, frequent communications between reviewers, tracking of reviews, and informing sponsors of the fact that an application will go through a consultative or collaborative review as soon as that decision is made. This new SOPP should help ensure that intercenter consultations occur in a more predictable manner.

In his remarks at the public hearing, Robert Nerem, a chairman of the external review subcommittee that conducted the review of CDRH for the FDA Science Board, discussed the evolution of a device from a simple scaffold to a scaffold with growth or chemotactic factors, to a third generation product to which cells are added. We agree with him that changing the jurisdiction over a such a product as it evolves “appears to be not only unwarranted, but an impediment to the evolution of this platform technology and the development of new products.” Certainly, the best way to assure appropriate and timely review of combination products that include established devices is to retain CDRH jurisdiction over their review. That is also the result required under the law, unless a device’s primary intended purpose, thus, its primary mode of action, is achieved by chemical or metabolic means.

5. Public Health Considerations Do Not Favor CBER Over CDRH. In most instances, public health impact is the principal consideration that informs FDA’s discretionary decision making. Public health considerations, however, to the extent they favor a Center for jurisdiction over wound dressings with cellular components, favor CDRH. First, as noted by many speakers at the public hearing, wound healing products that include cellular components have been safely marketed for years. Although vigilance against the potential for spread of contagious and zoonotic diseases is appropriate, the absence of any data linking these products to the transmission of infectious agents counsels against relying upon public health concerns to transfer jurisdiction. Not one presenter at the public hearing provided evidence of a public health problem with wound healing products; in fact, most stated unequivocally that there was no such problem. While presenters representing consumer groups expressed concerns regarding the novelty of cellular products and disease transmission, such risks and the appropriate state of the art controls are understood by the agency, including CDRH, and do not present new challenges merely because they are presented in the guise of a combination device-biologic rather than simply in a biologic product.

Second, CBER’s expertise in regulating products that may contain infectious agents provides an argument, but does not provide a basis, to upset the status quo for combination products with cellular components when compared to CDRH’s track record, regulatory authorities, and record of strong enforcement, which more substantially favor jurisdiction in the Center for Devices. As discussed above, premarket device authorities permit the evaluation of specific safety concerns before a product goes to market, and the QSR is no less strict in requiring, where appropriate, state of the art procedures to assure disease detection and prevention. In addition, medical device reporting, tracking, and post-market surveillance authorities allow the agency to identify and monitor potential

health risks, such as the spread of infectious disease, and would provide an early warning system for any public health issues presented by these products.

While CBER may exercise some of these authorities to a limited extent, CDRH has greater experience and comfort with their application. Further, CDRH, as the Center with primary responsibility for regulating medical sterilization products, has significant expertise in the transmission and control of infectious agents. Finally, should additional controls particular to biological products, such as lot release, be deemed necessary for a particular product or group of products, they can be made a condition of a device's clearance or approval by CDRH. In sum, no advantage exists to move wound dressings with cellular components from CDRH. While we acknowledge and take very seriously the general public health concerns with products that are derived from human tissue and cells, such concerns are associated to date only in theory, and not in fact, with the wound healing products at issue. In other words, CDRH has fully protected the public health with its careful and thorough regulation of wound dressings with cellular components.

As wound dressings that incorporate cellular components continue to develop, the metabolic component may overtake the structural component in contributing to the product's primary intended purpose, or advances in the matrices of such products may result in highly effective scaffolding devices that work almost exclusively structurally. When changes in technology lead to clear changes in the primary mode of action of these products, the statutory analysis discussed in section I of this comment should govern jurisdiction.

II. APPLICATION OF APPROACH TO WOUND DRESSINGS THAT INCORPORATE LIVE CELLULAR COMPONENTS

The approach set out in this comment provides a workable means of determining jurisdiction for wound dressings that are currently on the market and similar products that may evolve. Under this approach, combination wound healing products that incorporate live cells should remain under CDRH jurisdiction, unless the live cells can be demonstrated to be the primary means by which the product achieves its primary intended purpose. The agency's own position in the final rule establishing registration and listing for human cells, tissues, and cellular and tissue-based products ("HCT/Ps"), 66 *Fed. Reg.* 5447 (Jan. 19, 2001), supports such a position. In determining that skin allografts could be regulated without premarket review because they were not dependent on the metabolic activity of living cells for their primary function, the agency stated that skin allografts "may contain living cells, but do not depend upon them for their primary function, which is structural." *Id.* at 5459-5460. Thus, a product which functions like

¹⁰ Such concerns are again at the forefront due to the recent recall by CBER of tissues processed by Cryolife, Inc., after Cryolife failed to adequately correct regulatory violations found by CBER. There is no basis for any suggestion that the inherent risks of products derived from human tissues and cells are or would be exacerbated under CDRH regulation. CDRH's regulatory authorities and track record demonstrate its ability to protect the public health from the spread of infectious disease related to such products. Indeed, the Cryolife recall illustrates that no Center is perfect in its regulation of such risks.

skin, even if it contains growth factors or live cells, performs a structural function, which is clearly a device purpose.

In some instances, the live component of the product may make an equally significant or greater contribution to the overall functioning of the product. The statute may require such a product to receive reviews under both device and biologics authority; however, because the FDC Act definition of a device controls over the PHS Act definition of a biological product, *see* pages 7-8, *supra*, jurisdiction over this product lies in CDRH. Additional factors that support CDRH's jurisdiction over such a product include the need for predictability and consistency, which is particularly important to the small companies that are often responsible for innovations in this area. These interests are best served by maintaining historical jurisdictional assignments, and the experience with the issues raised by these products and with the appropriate regulatory authorities to control potential risks associated with these products. In the absence of a public health reason, which neither FDA nor any private party has yet articulated, even many combination products with significant metabolic activity should continue to be regulated by CDRH.

III. OTHER COMBINATION PRODUCTS

A. The Statute Requires a Unified Approach

The agency has requested comments on regulation of device matrices that incorporate living human cells and similar products, stating that “[s]ingle entity products, combination products containing bone, ligament and vascular products used for structural purposes, and drug-device combination products” are beyond the scope of the current opportunity for comment. *May Federal Register Notice*. All combination products, however, are subject to the same statutory provision; any effort to apply one construction of section 503(g) to wound dressings and a different construction to other combination products would be arbitrary, capricious, and not in accordance with law. *See* 5 U.S.C. § 706.

Further, although the statute only addresses combination products, the logic of section 503(g) extends to other products that cannot be readily classified as single-product entities.¹¹ Indeed, the assignment of combination products under section 503(g) is based on the respective expertise of FDA's Centers in regulating devices, drugs or biologics. In other words, Congress created a system of premarket review assignment, which mimicked the expected regulation of single entity products that were drugs, devices, or biologics. Products such as cellular and tissue implants, and encapsulated cells or tissues do not meet the definition of combination product, but implicate the definitions of a biological product and a device. Although the functioning of these products may be indistinguishable from a conventional bandage, the *InterCenter Agreement Between CBER And CDRH* (October 1991) assigns jurisdiction over the products to CBER. The jurisdictional determination for these products seems to reflect

¹¹ When FDA implemented section 503(g), the agency developed procedures that applied to both combination products and products for which “jurisdiction is unclear or in dispute.” *See* 21 C.F.R. § 3.1.

an overly rigid approach that any product incorporating a cell is within CBER's purview, an approach that overlooks the legally central concept in FDA regulation, namely, intended use.

In enacting section 503(g) of the FDC Act, Congress sought to create greater certainty and eliminate delays in product review caused by the need to engage in complicated jurisdictional analyses for each combination product. *See S. Rept. No. 101-513, 30 (Oct. 9, 1990)*. This purpose is best served by adopting a rational and legal approach to the regulation of combination products containing live cellular components and extending that approach to all combination products and other products potentially subject to regulation by more than one FDA component.

B. Consistent with the Above Approach, There Should be No Question that Acellular Wound Healing Products with Deactivated Cells or Inherent Growth Factors Will Remain at CDRH

Just as acellular wound healing products are devices and should remain in CDRH, the presence of deactivated cells on a matrix, as in Advanced Tissue Sciences TransCyte® product, or the presence of inherent growth factors on a porcine matrix, such as in Cook's Oasis SIS wound healing products, should not result in a change in product jurisdiction, where the acellular matrix remains the primary element necessary for achieving the structural and protective purpose of the device. Further, accurately describing and characterizing any enhancing activity resulting from the presence of cells, growth factors, or other biological product constituents should not result in a change of jurisdiction, as long as their contribution is not demonstrably primary to achievement of the product's intended purpose. We request that one specific outcome of this process be a definitive statement by the agency that acellular wound healing products, including those that contain deactivated cells or inherent biological components like growth factors that aid in the wound healing purpose, will remain under CDRH jurisdiction.

C. Other Products Traditionally Regulated by CDRH Should Also Remain in CDRH

Because the statute requires FDA to develop a single regulatory scheme for combination products, the agency must consider the consequences a scheme intended for wound dressings with cellular components could have for other combination products. Several products that are devices may receive enhancement from the addition of live cells, including products of the types that have for decades been subject to the expertise of CDRH reviewers, such as:

- vascular and neural grafts
- replacement heart valves and cardiac patches
- spinal and mandibular prosthetics
- tendon and ligament grafts
- urethral and intestinal support and repair devices.

To switch the regulation of a heart valve from CDRH to CBER merely because the next generation of valves are lined with epithelial cells that serve to speed the integration and functionality of the valve would create a gap in the knowledge and experience with such devices that could in and of itself threaten the integrity of approved devices, thus endangering the public health.

Such a gap in institutional capability would also impede product development and approval as CBER worked to replicate device review resources and get up to speed, thereby further adversely affecting the public health. The actual cost in dollars and in wasted resources for moving devices from CDRH to CBER is far more significant than the potential cost of consults with CBER, or outside consultants, during the premarket review process of devices that are enhanced with cellular components late in their development process. Thus, eschewing CDRH's familiarity with the interaction of biological components and devices from its extensive experience in regulating implanted devices would not be in the public interest and would serve no rational or legal regulatory imperative.

D. The Agency Must Follow Appropriate Procedures Under the Administrative Procedure Act

Because of the broad effect on the regulation of all combination products in general of any policy adopted for the regulation of wound dressings, the agency must implement any change in its current approach to regulation using appropriate procedures. The need for transparency and uniformity favors a rulemaking for any approach the agency adopts. While Cook appreciates the public hearing held by the agency and this opportunity for comment, the hearing and comment period do not relieve the agency of any of its responsibilities under the Administrative Procedure Act ("APA"). FDA participants at that hearing made clear that they viewed the forum as a "listening session," and did not put forward a proposal for the regulation of these or other combination products. The APA requires an opportunity for meaningful comment before a rule with the effect of law can take effect, which can only occur when interested parties have reviewed and responded to a proposal. *See, e.g., Florida Power & Light Co. v. United States*, 846 F.2d 765 (D.C. Cir. 1988) (requiring sufficient factual detail and description of rationale to permit meaningful comment). Thus, the agency must issue a proposed rule, solicit comments, and publish a statement of basis and purpose before implementing any approach to the regulation of wound dressings or other combination products that does more than interpret "primary mode of action" and other relevant statutory provisions. Further, although agencies are not required to use rulemaking to implement mere interpretations of statutory language that do not impose additional procedures, such as the interpretation advocated in this comment, Cook believes that given the uncertainty surrounding the regulation of combination products, FDA should promulgate a regulation under section 553 of the APA regardless of how the agency responds to comments given at the public hearing and during this comment period.

Other potential approaches could amount to legislative rules, and thus require notice and comment procedures. For example, moving all cell based combination products to CBER would at a minimum require notice and comment rulemaking. *See Associated Builders & Contractors, Inc. v. Reich*, 922 F.Supp. 676 (D.D.C. 1996) (rule that deprives agency of discretion to make a case-by-case determination is legislative and subject to notice and comment procedures); *see also Connecticut Dept. of Children and Youth Services v. DHHS*, 9 F.3d 981 (D.C. Cir. 1992) (rule that fills a gap in statutory language is a legislative rule). This approach, however, would disregard the statutory directive that FDA assign jurisdiction over combination products according to their primary mode of action, and would irrationally delineate policy for a narrow category of products that, by statute, belong to a broader category governed by different requirements. As a result, we are skeptical that any amount of process could legitimate such an approach.

III. CONCLUSION

The current uncertainty over the proper regulation of wound dressings with live cellular components reflects an intent to change how FDA has implemented its understanding of primary mode of action. However, the changes to the device and drug definitions that accompanied section 503(g) make clear that certain jurisdictional decisions over combination products require only that the agency address the threshold question of whether a combination product is a drug, device, or a biological product. If the product considered as a whole meets one of these definitions without qualification, the inquiry is at an end. If one component of a combination product does no more than enhance the effect of another component, and thus is secondary in nature, the primary contributor, in light of the product's "primary intended purpose[]," will determine jurisdiction.

In rare cases, the analysis will be more difficult, *i.e.*, with combination products that achieve their therapeutic effect by means of two or more significant contributing actions, and two reviews may be deemed necessary. In such rare cases, other factors may appropriately be considered in determining the Center with primary jurisdiction over the product, particularly factors related to the Congressional purpose in enacting section 503(g). One important factor is the agency's historical approach, as manufacturers are likely better able to anticipate the entity with jurisdiction over their product by looking at jurisdictional decisions concerning predicates or other similar products than by engaging in a primary mode of action analysis which will not yield meaningful results. Another factor applicable to all combination products is the cost to the agency and industry of switching jurisdiction over products that have been regulated for years in one Center, which is the repository of the agency's institutional knowledge and expertise, and in which industry has invested time and resources to achieve specific regulatory compliance and to educate reviewers on their product technologies.

For devices, this latter factor becomes particularly stark as industry looks ahead to the incorporation of live cells into even more complicated and critical devices, such as

cardiac and orthopedic grafts and implants. Most device companies are small, particularly those involved in tissue engineering. These companies have invested in educating CDRH over the course of many device iterations in their technologies, and in clinical development programs and manufacturing processes that comply with device authorities. This investment and the harm to the industry of a switch in regulatory authority, coupled with the cost of replicating device expertise in CBER, argues for maintaining the status quo for products that have been regulated as devices, especially when no public health concerns regarding the products are evident. Further, the swift pace of device evolution requires regulatory processes that are flexible and responsive. Therefore, as recognized by the Report to FDA's Science Board, premarket review implemented by CDRH is more likely to be effective in dealing with evolving therapeutic technologies such as device-biologic combinations.

In sum, the agency's decision here has important ramifications for the future and should not be made in a vacuum. The analysis made in this comment should apply equally to wound dressings with biological components, other combination products, and single entity products for which jurisdiction is unclear. The agency is legally bound to a single standard, and cannot rationally defend applying a standard in one fashion to wound dressings and in some other fashion to other combination products. Further, because of the similarities in issues raised by certain single entity products, the agency should apply the same analysis to these products, thus creating a unified regulatory approach to a class of products that raise similar regulatory issues. Lastly, considering the potential impact of the agency's decision, we believe any new FDA approach to regulating combination products should, at a minimum, be subject to notice and comment rulemaking. However, assigning all combination products that contain live cells to CBER would contravene the statute by disregarding the statutory directive that FDA assign jurisdiction over combination products according to their primary mode of action, and therefore would be an impermissible outcome of any administrative process.