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

Re: Docket No. 02N-0445

To Whom It May Concern:

We are writing to comment on the issues presented in the *Federal Register* Notice announcing the U.S. Food and Drug Administration's ("FDA's") November 25, 2002 public hearing on combination products. *See* 67 Fed. Reg. 65,801 (Oct. 28, 2002). We are primarily commenting on the second group of questions asked by the agency,[1] on determining "primary mode of action" for combination products; however, our comments also address whether a single or separate applications should be required, which is covered by the fourth group of questions.[2]

I. Introduction

We previously commented on the proper determination of primary mode of action for combination products in comments we submitted to Docket No. 02N-0169 (soliciting comments

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[1] The second group of questions is:

> What factors should FDA consider in determining the primary mode of action of a combination product? In instances where the primary mode of action of the combination product cannot be determined with certainty, what other factors should the agency consider in assigning primary jurisdiction? Is there a hierarchy among these additional factors that should be considered in order to ensure adequate review and regulation (e.g., which component presents greater safety questions)?

[2] The fourth group of questions is:

> Recognizing the need to ensure product safety and effectiveness, what criteria should FDA use to determine whether a single application or separate applications for the individual components would be most appropriate for regulation of a combination product? For example, FDA may determine that it is necessary to apply elements of different regulatory authorities to a combination product to ensure safety and efficacy (e.g., device postmarketing reporting for the combination product, with drug current good manufacturing practices (CGMPs) applicable to the drug component only). Should the need to apply a mixed regulatory approach influence whether one application or two are more appropriate?

on the jurisdictional classification, assignment, and premarket review of combination products that consist of autologous or allogeneic living cells combined with a device matrix for wound healing, *see* 67 Fed. Reg. 34,722 (May 15, 2002)) and incorporate those comments herein by reference. Because we believe strongly that a comprehensive, coherent policy for the regulation of combination products is critical to the successful development and efficient approval of device/drug and device/biologic combinations, we are summarizing and restating our previous comments here to address the determination of primary mode of action for device combinations more generally.[3] These comments also address some statements made by speakers at the November 25th public hearing that we believe incorrectly analyze combination product law.

Importantly, we believe any change in interpretation of primary mode of action by the agency should be made through notice and comment rulemaking. Although mere agency interpretations of statutory language do not require the use of rulemaking when they do not impose new requirements, given the importance of the regulation of combination products to the public health, the agency should issue a proposed rule, solicit comments, and publish a statement of basis and purpose before implementing any new approach to combination product regulation.

II. FDA must determine primary mode of action according to the dictates of the statute

Most presentations at the meeting did not address primary mode of action. The few that did address the issue did not address the critical question, what does the law require? Some comments, we believe, were simply wrong, such as those that focused on combination products as being a separate product category under the statute that should be subject to its own premarket and postmarket regulations and guidance and those that viewed risk as the proper driver of which Center should regulate the product. In determining primary mode of action, the principal inquiry is what is the product's jurisdictional identity? That is, which of the three definitions—drug, device or biologic—does the product as a whole meet? Jurisdictional identity is tied to a product's primary intended purpose, and thus its primary mode of action. Therefore, to determine how a combination product should be regulated one must ask what is the primary intended purpose of the product, and how does it achieve that purpose, *i.e.*, does it primarily achieve its primary intended purpose by chemical or metabolic means? If not, it should be regulated as a device. This fundamental point was not focused on by any of the speakers, including those who used drug/device combinations as the starting point for their remarks.

A. Primary mode of action is the principal issue that FDA must address

Simply put, primary mode of action is the fundamental issue that must be resolved before the other issues raised by FDA for purposes of the November meeting become relevant. Section 503(g) of the Federal Food, Drug, and Cosmetic Act (the "FDC Act")[4] requires FDA to

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[3] For the same reason, we believe FDA should delay any action on a jurisdictional determination for combination products intended for wound healing until a more comprehensive policy is developed.

[4] Section 503(g) provides in relevant part:

> (1) The Secretary shall in accordance with this subsection assign an agency center 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 – . . .
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> (A) a drug (other than a biological product), the agency center charged with premarket review of drugs shall have primary jurisdiction, or

determine the "primary mode of action" of a combination product, *i.e.,* whether the combination product acts primarily as a drug, device, or biological product, and to assign premarket review jurisdiction accordingly. Congress intended this provision to establish "firm ground rules" to ensure consistent, predictable treatment of combination products. *See* S. Rep. 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).

B. Under the law, primary mode of action is determined by how a product achieves its primary intended purposes

The first question posed by FDA on primary mode of action in the October *Federal Register* Notice was "[w]hat factors should FDA consider in determining the primary mode of action of a combination product?"

1. The simple answer is that section 503(g) and the jurisdictional definitions for devices, drugs, and biologics dictate how primary mode of action is determined.

Although Congress did not provide an explicit definition of "primary mode of action", Congress intended its meaning to be understood by reading section 503(g) with the conforming amendments to the definitions of "drug" and "device" in the Safe Medical Devices Act of 1990 ("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). As a result of those amendments, the definition of device determines whether a device/drug or device/biologic combination product must be regulated as a device, drug or biologic. Specifically, section 201(h) of the FDC Act defines "device" as:

> 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.

(B) a device, the agency center charged with premarket review of devices shall have primary jurisdiction, or
(C) a biological product, the agency center charged with premarket review of biological products shall have primary jurisdiction.

The final clause of the device definition provides a means for distinguishing devices from other FDA-regulated products. Devices do not achieve their "primary intended purposes" through drug-like or biologic-like action, *i.e.*, through chemical or metabolic action in or on the body. However, a product may be a device even if it includes a drug or biologic component that acts in or on the body, if the drug action is secondary to the device effect.

2. The SMDA substituted the words "its primary" for the phrase "any of its principal" in paragraph (3) of the device definition to ensure a clear understanding that secondary metabolic or chemical effects do not void a product's device status.

This change, and a change to the drug definition[5], were made to ensure that the jurisdictional bases for regulation and the internal review assignment mechanism set forth in section 503(g) were consistent. Thus, the SMDA definitional changes make clear that the terms "drug" and "device" encompass products that act on the body in more than one way, but achieve their primary intended purposes through drug or device mechanisms. 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.[6]

3. This view is fully supported by FDA's Federal Register document announcing the agency's approach to implementing SMDA.

In implementing the SMDA 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 Fed. Reg. 14,111, 14,112 (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.

In sum, the first, and often the definitive, step in determining the primary mode of action of a device/drug or device/biologic combination product is to evaluate the product's primary intended purpose. If it is a purpose that is not primarily achieved through metabolic or chemical action in or on the body of man, then the Center for Devices and Radiological Health ("CDRH") should regulate the product as a device, with appropriate consults. 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

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[5] Congress amended section 201(g)(1)(D) of the FDC Act 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" to ensure that articles that primarily worked through chemical or metabolic means could be drugs despite a secondary device effect.

[6] 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 Public Health Service Act ("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).

the product types regulated by FDA, jurisdiction should be assigned to the Center with authority over that product type.[7]

C. The statute does not require a comparison of a combination product's components; it requires a determination of the product's legal jurisdictional status

In its May *Federal Register* Notice for the August meeting on combination wound healing products, 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." While FDA did not repeat this suggestion in its October *Federal Register* Notice, we are concerned that this view continues at the agency and may also be reflected in other submissions to the docket. When applied to device/biologic combinations, this analysis invites a determination of a product's activity at the cellular level, and ignores how the "primary intended purposes" of a product are achieved. *See* § 201(h) of the FDC Act. For example, magnifying the importance of the presence of tissues or cell-based components in a combination product will result in an inappropriate comparison of dissimilar things, *i.e.*, the product's primary intended purposes with the individual significance of each secondary component that may aid in healing (*e.g.*, cellular material added to a device matrix with a bandaging 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 or chemical action of a drug or biological product may enhance the therapeutic effect of a device, at the cellular level, structural and metabolic or chemical activities may be so closely entwined that focusing on them can divert the agency from appreciating the product's primary intended purpose. The relationship of the two components in achieving the product's intended purpose is likely to be clearer than the relationship of the two in achieving a cellular effect. Thus, by positing cellular activity as the basis to determine premarket review assignments, FDA overlooks the jurisdictional identity of combination products, which is tied to the key regulatory concept of primary intended purpose. Simply put, 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.

D. Combination products are not a separate jurisdictional product type and must be regulated according to the FDC Act's jurisdictional product definitions

A few speakers at the November 25th hearing suggested that combination products were a fourth type of product. We believe these comments are distracting and unhelpful. One speaker

[7] Although under the PHS Act, biological products are not defined by mode of action, sections 201(h) and 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. *See* section III, *infra*.

argued that certain combination products, while traceable to their constituent jurisdictional parts, served only one function and therefore should not be looked at as combinations at all, but as "single entity products." This same speaker argued that combinations had been recognized as a separate "fourth" kind of product by section 416 of the Food and Drug Administration Modernization Act of 1997 ("FDAMA") and that the FDC Act thus did not require the agency to force such a product into one of the other three categories. Another speaker agreed and suggested combination products should be subject to their own distinct regulatory regime.

We disagree with these speakers because combination products are by definition products with multiple regulated constituents whether or not they are legally devices, drugs, or biologics. Further, there is no support in the FDAMA legislative history for the view that combination products were intended to be regulated as an independent jurisdictional entity. FDAMA merely codified in the statute the combination product designation procedure in Part 3 of the regulations, and recognized, as does Part 3, that jurisdiction may be as unclear for single entity products as it is for combination products. Similarly, the designation of a product as a "combination product" by the new Office of Combination Products established by the Medical Device User Fee and Modernization Act of 2002 has no independent regulatory significance except that the lead Center must be assigned based on primary mode of action. To the extent a combination product is, for example, made up of a device component that is responsible for its primary intended purpose and a drug component with a secondary effect, legally the product is a device. The fact it is also a combination product is of no practical significance to its pre- or post-market regulation.

III. When a determination of primary mode of action cannot be made, FDA should look to the historical regulation of the product, the potential impact of a jurisdictional change on the affected industry, and for device/biologic combinations, to the statutory preference for devices over biologics

In the October *Federal Register* Notice, FDA also asked what factors should be considered "where the primary mode of action cannot be determined with certainty." In almost all instances, a primary intended purpose analysis will yield rational product jurisdiction determinations. In the rare instances where this does not yield clear results, more than one approval may be necessary for the same product. However, in keeping with the Congressional goal of streamlining the review of combination products, the agency should, whenever possible, avoid requiring premarket reviews by multiple Centers for a single product.[8] Rather, the agency should rely on other relevant considerations to determine the lead Center for these products.

A. Historical product determinations should be given significant weight and the impact on industry of a jurisdictional change should be considered

Consistent with the Congressional goal of ensuring predictability and consistency, where a type of product has been historically regulated as a single entity in one Center, the agency still should assign jurisdiction for such products to that Center when a component is added that has a different jurisdictional identity and primary mode of action cannot be determined. To do

[8] The concern is to avoid two independent regulatory clocks. We fully support using consults as a means of ensuring full, quality reviews with lead jurisdiction in one Center.

otherwise would result in a critical loss of existing agency expertise to the premarket review process, thus wasting agency and industry resources and likely prolonging reviews. Of course, a consult with the other Center(s), or in rare cases, more than one approval may be appropriate, but in this instance would still result in significant inefficiencies.

Indeed, maintaining jurisdiction in the Center that has historically reviewed a product which is then combined with another type of product is important because the impact of regulatory change on industry, especially smaller industry players in the device and biotech worlds, would be significant. Such companies have invested their resources in meeting Center expectations and educating Center staff about their products. Companies plan product development paths for years into the future based on the expected regulatory regime for their product. A disruption in jurisdiction would be especially difficult for device manufacturers who have rapid development cycles and rely upon a predictable and responsive regulatory process and reviewers familiar with their products to achieve quick market entry for innovations and updates to their products. Moreover, based on current law and reasonable expectations, companies invest heavily in quality systems and postmarket surveillance programs. An unnecessary change in Center jurisdiction would create costs that the agency cannot justify.

B. Absent a history of safety problems with a product type in a particular Center, safety is not a helpful consideration in determining the regulatory path for a product

Contrary to some of the speakers at the November meeting, we do not believe that safety is a primary consideration that should tip the product jurisdiction balance, absent a history of safety problems for products regulated in a particular Center that are substantially the same as the combination product in question. In general, we agree with speakers who disputed that safety should be a primary issue and stated that the premarket paths and postmarket authorities available to each Center assure that the agency can obtain the data necessary to determine the safety of combination products no matter the Center jurisdiction. We believe, however, that for combination products with device components, the device authorities provide the flexibility and least burdensome approach that will best assure all the proper controls are in place to assure safety and efficacy and will also allow for efficient and effective reviews that will encourage product development.

1. The device premarket processes provide flexible and comprehensive regulation of safety and effectiveness for combination products.

For example, the premarket approval ("PMA") process provides the flexibility and interactive opportunities (pre-Investigational Device Exemption submission meetings, pre-PMA meetings, and 100 day meetings) necessary to design a clinical development program that will provide the data necessary to thoroughly understand and approve complex combination products. Further, the availability of the Humanitarian Device Exemption pathway to market, which has no analog in drug or biologics regulation, has resulted in new technologies becoming available to patients for whom no available therapies have worked.

2. The Quality System Regulation's flexibility and emphasis on design controls provides assurance of safety and effectiveness for combination products.

Similarly, the device Quality System Regulation ("QSR") provides a flexible framework for the manufacture of combination products that emphasizes design and process controls and validation. Indeed, pre-production design controls are critical to the intrinsic safety and effectiveness of medical devices, and thus to combination device/drug and device/biological products. Not only do current good manufacturing practices for drugs not include design controls, the other Centers' investigators 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 other types of products in the future, *e.g.,* drug coated implants, and structural devices incorporating live cells.[9] Further, the QSR requires 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.* 52,602, 52,603 (Oct. 7, 1996). Therefore, the appropriateness of the QSR to device regulation and the ability of manufacturers to incorporate design and manufacturing controls necessary to the safety and effectiveness of other jurisdictional components makes assigning jurisdiction for device combinations to CDRH especially appropriate when the primary intended purpose of a product is not achieved by chemical or metabolic means.

3. CDRH's experience with combination product regulation and least burdensome approach are important to the development and approval of combination products.

Moreover, in addition to its flexible, comprehensive, and interactive premarket and postmarket authorities, CDRH has extensive experience in regulating combination products.[10] We agree with the comments of Robert Nerem, chairman of the external review committee that conducted a review of CDRH for FDA's Science Board, who spoke at the August meeting on combination device/biologic products for wound healing, that changing Center jurisdiction over products as they evolve is not only unwarranted, but stands as an impediment to new product development. The best way to assure appropriate and timely review of combination products that include devices consistently regulated by CDRH is to retain CDRH jurisdiction. Unless a combination device product's primary intended purpose is achieved by chemical or metabolic means, that is also the result required under the law.

C. For device/biologic combinations, the statute prefers jurisdiction in CDRH

When a biological product is both a biologic and device, the FDC Act defines the product as a device. Specifically, section 503(g) supports the conclusion that CDRH has jurisdiction

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[9] 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).

[10] 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).

over combinations that are both devices and biological products. The FDC Act limits CDER's jurisdiction to any combination products that constitute a drug "other than a biological product," however, 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 must be assigned as the lead Center to review and approve the product.

IV. The Agency should use notice and comment rulemaking in interpreting "primary mode of action"

Finally, because any new agency interpretation of primary mode of action will have such significance for the regulation of combination products, we believe notice and comment rulemaking is appropriate. Indeed, if the agency's approach results in the imposition of new requirements, notice and comment rulemaking will be required. However, any approach to assignment of Center jurisdiction must take into account the jurisdictional product definitions and the primary intended purpose of combination products. If not, even notice and comment rulemaking will not legitimize the agency's approach.

V. Conclusion

The changes to the device and drug definitions that accompanied section 503(g) make clear that jurisdictional decisions over combination products require that the agency address the threshold jurisdictional 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, the inquiry is at an end. Thus, if one component of a combination product merely enhances 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. However, multiple reviews in different Centers should be avoided and other factors may appropriately be considered in determining the Center with primary jurisdiction over the product. One important factor is the agency's historical approach upon which manufacturers relied to plan their product development. Another factor 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 FDA'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. Another factor of special importance for combination products incorporating devices is the flexibility and comprehensiveness of the device authorities, which provide necessary and adequate controls to assure the safety and effectiveness of the device component as well as the other combination product constituents. When primary mode of action cannot be determined because of complementary action, CDRH's effectiveness should be considered in selecting a lead Center.

Finally, we suggest that the agency continue to develop policies for combination products with full public participation, which to be meaningful, at least on the critical and fundamental issue of primary mode of action and Center assignment, should be done through notice and comment rulemaking. We also agree with the meeting participants who suggested that the agency should hasten its effort to provide guidance in this area by timely publishing the results of requests for designation as jurisdictional updates, and by also making available summaries for historical determinations.

We appreciate the opportunity to comment further on the critical issue of combination product regulation and look forward to the agency's response.

Sincerely,

Stephen L. Ferguson/mat

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