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Mark B. McClellan, M.D., Ph.D.
Commissioner, U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857-0001

Re: FDA's Interpretation of Section 503(g) of the Food, Drug, and Cosmetic Act (Combination Products)

Dear Dr. McClellan:

My client and I are very concerned about information we recently received from the Agency concerning the regulation of "combination products."

My understanding is that a non-biologic, health care product that achieves its primary intended use through a mode of action that does not require chemical action within or on the body, or a metabolic process, is to be regulated as a device. My understanding is that this is true regardless of whether the article is a single item or a "combination product."

We have seen some evidence that the Agency is prepared to act otherwise, and thus take a significant step backward in the proper regulation of combination products.

During a meeting on March 17, 2003, we learned that the Agency may take the position that there are provisions in the Food, Drug, and Cosmetic Act (FDCA) which will allow the Agency to arbitrarily regulate as drugs either those products otherwise defined as devices, or defined as device-based combination products. Such an interpretation would undoubtedly be contrary to congressional intent, and it would threaten what was meant to serve as a consistent methodology for determining how a combination product is to be regulated, i.e., as a drug or device. Moreover, it could force certain devices to undergo a process of premarket evaluation far in excess of what is legally appropriate, or what is needed for public protection.

**The purpose of this letter is to request that you reaffirm that any non-biologic, health care product, or combination product, that does not achieve its primary intended use through chemical action within or on the body, or through metabolic action, will be regulated as a device or a device-based combination product.**

## The Specific Device in Question

The issue we are raising pertains to all health care products, but the specific product in question can be used to help clarify the issues.

**We are not writing to convince you that we are correct in our description of the device's primary intended use or mode of action. We believe that should be done through the designation process provided by Part 3. We are writing because we learned at our March 17 meeting that the Agency may treat The Product for use as drug for reasons unrelated to the applicable provisions of the FDCA.**

**The Pending Interpretation**

During our March 17 meeting, the Agency noted that the Center for Drug Evaluation and Research (CDER) had more expertise related to The Product than the Center for Devices and Radiological Health (CDRH); the implication being that such a consideration should influence the determination as to whether a product is a drug or device. Of course, it should not. The FDCA explicitly provides for intercenter consultation. Thus, either CDER or CDRH can participate in a review, regardless of whether the combination product is a drug or device.

We learned that The Product may be treated as a drug because . This fact, however, has no apparent bearing on whether The Product is a drug or device.

The interpretation of the statute that would purportedly allow the Agency to make such arbitrary decisions is described below. The interpretation is not in the interest of the public, and is clearly contrary to the FDCA.

**Public Health Interests**

There are currently no in commercial distribution. The health care facilities that for this purpose. to patients. Alternatively, some health care facilities My client hopes to market The Product with an explicit labeled indication . Doing so will allow physicians to safely their patients using high quality s intended for that purpose.

The use of these is the basic standard of care in . Fortunately, the device regulatory process offers the opportunity of obtaining the e 510(k) process. We presume, in this instance, that a 510(k) clearance would require the submission of information pertaining to the

constituents of the device. It is far more uncertain what would be required as the legal standard for approval of the product as a drug. This illustrates the importance of properly categorizing a combination product as a device when it meets the definition.

This is not to imply that devices are inadequately regulated – only that the regulatory process, as intended by Congress, is more flexible.

**Related Provision of the FDCA**

Section 503(g) of the FDCA states that when a regulated product consists of both a device and drug component, the Agency will determine "the primary mode of action" of the combination product. It further states that if the primary mode of action is that of a device, the product will be regulated by the "person" responsible for the premarket review of devices, i.e, CDRH. Section 201(h) of the FDCA contains the definition of a device. This definition includes a description of a device's mode of action. In partial summary, it says a device is an apparatus, including any accessory or component, intended to treat a disease and which:

> ...does not achieve its primary intended purposes through chemical action within or on the body .. and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

A dispassionate interpretation of these provisions is that a product's primary mode of action is the mode of action associated with the product's primary intended use. If this primary mode of action does not employ chemical action within or on the body, and does not require metabolic activity, the product is to be regulated as a device by CDRH.

The Agency appears to have been operating for the past thirteen years in conformance with this interpretation, with one general exception. Although it appears that it could, the Agency has not used these provisions to permit the marketing of a device-based combination product through a device-related premarket review program alone when the product contains a drug component that is not otherwise available under the programs used to regulate drugs. In general, the Agency requires that the drug component of a device-based combination product have a drug-regulation-based clearance for a use that is consistent with the use for which the drug component has been incorporated into the device. Aside from this reluctance to use a premarket notification, or a premarket approval application, to clear a new drug entity or a new use for an existing drug entity, the Agency has interpreted the provisions as described above. If there have been occasions when a drug or device decision seems contrary to this interpretation, it appears that there may have been a dispute about a product's primary intended use or mode of action. We are certainly not aware of any apparently anomalous decision being based on an overt Agency rejection of the accepted statutory interpretation. The Agency has successfully utilized the Section 503(g) provisions to bring some order and predictability to the drug versus device decision-making process.

To help bring order, the proper interpretation of these provisions has been amplified in related Agency guidance documents, e.g., The Intercenter Agreement Between The Center for Drug Evaluation and Research and the Center for Devices and Radiological Health. Section VIII A.5. states:

> A device containing a drug substance as a component with the primary purpose of the combination being to fulfill a device function is a combination product and will be regulated as a device by CDRH.

Section VIII A.5. states:

> A liquid, powder, or other similar formulation intended only to serve as a component, part or accessory to a device with a primary mode of action that is physical in nature will be regulated as a device by CDRH.

Section VIII A.3. states:

> The phrase 'within or on the body' as used in 201(h) of the Act does not include extra corporeal systems or the solutions used in conjunction with such equipment. Such equipment and solutions will be regulated as devices by CDRH.

These statements in the FDA guidance are consistent with the statutory interpretation described above. But now, we are informed that someone in the Agency is reconsidering the Agency's position.

**The Purported Exception**

The combination product provision [Section 503(g)] was added to the FDCA by the Safe Medical Devices Act of 1990 (SMDA). SMDA also changed the definition of a drug [201(g)] and the definition of a device [210(h)].

Although the wording is flawed (discussed below), the device definition was changed to indicate that a product is a device if its primary intended use is achieved without chemical action in or on the body or through metabolic action. Prior to the change, if any of a product's principal intended uses were achieved with chemical action within or on the body or through metabolic action, the article became a drug (or should have).

SMDA also eliminated from the Section 201(g)(1) portion of drug definition the phrase "but does not include devices or their components parts or accessories."

We were informed in our March 17 meeting that it was the elimination of this phrase that has muddied the waters (after thirteen years) of the drug/device rules and, that because of this change, a product that is otherwise a device can be regulated as a drug. Unfortunately, no one described the circumstances under which the Agency would choose to do so.

I regret to observe that such an interpretation shows an absence of familiarity with the value of the prevailing interpretation and with Congressional intent. With respect to the latter, it is not just off the mark – it is directly contrary to the intent of Congress. This assertion is based upon my personal knowledge, and upon a review of the record. I was the Director of the CDRH's Office of Device Evaluation when the SMDA was enacted. I helped formulate a number of the provisions of the SMDA, and I fully understand the intent of Congress with respect to most of its provisions. Much more important, a mere reading of the Congressional bill reports will show that removing the last phrase of 201(g)(1) was meant to support the rules enacted by Section 503(g), not call them into question.

The definitional changes enacted in 1990 were designed to create a clearer distinction between drugs and devices and to ensure that devices would not be regulated as drugs. The drug definition was modified in order to make it clear that FDA has authority to approve a combination product. In other words, to make the definition of a drug consistent with the newly enacted Section 503(g). The thinking was, that by removing the phrase, it would be clear that FDA could approve a drug that had a device component and that FDA could approve a device that had a drug component, without there being a simultaneous, distinct approval of the secondary component in the combination product. (As noted above, FDA operates this way unless a secondary drug component in a device-based combination product is not yet approved through a drug-based regulatory instrument.) The change was not intended to call into question the new combination product provision or the new device definition that was simultaneously enacted. It was to further reinforce the Agency's ability to use these provisions. To now say that the change in the drug definition made the distinctions between a drug and device less clear turns the work of the Congress on its head.

**History of Drug Device Definitions and Congressional Intent**

Before passage of the Medical Device Amendments to the FDCA in 1976, as now, drugs were defined in Section 201(g) and devices were defined in Section 201(h). The drug definition included a phrase that said "but does not include devices or their components parts or accessories." But there was no clear distinction between these articles. In 1976, The Report by the Committee on Interstate and Foreign Commerce on H.R. 11124, explained the problem very well:

> Existing statutory definitions of 'device' and 'drug', although legally mutually exclusive, are functionally overlapping and, thus, confusing to the device industry, the general public and the courts. ...The Committee proposal ends the existing definition of 'device' in section 201(h) ...to draw a clear distinction between a 'device' and a 'drug.' ...The new definition retains ...existing law that a device is an article ...intended to affect the structure or any function of the body ...These characteristics, which also are used in the definition of a 'drug' ...are modified by the proposed legislation to include the distinction that an article is a device if

> it 'does not achieve any of its principal intended purposes through chemical action within or on the body ... and is not dependent upon being metabolized for the achievement of any of its principal intended purposes.' This distinction means that the articles dependent upon chemical action or being metabolized, and otherwise falling within the definition of 'drug' in section 201(p) [h], are to be regulated as drugs and not devices. Thus, the proposed new definition of 'device' removes the gray area that exists under present definitions of 'drug' and 'device'. [Pages 13 and 14.]

The Congress was intent upon making a clear distinction between the two products, but their efforts did not create the clear distinction they had hoped for. The phrase " achieve any of its principal intended purposes" led to trouble. For example, if a catheter contained an antimicrobial coating designed to maintain the product's integrity over time, it could be considered a drug even though the catheter's primary purpose was to serve, for example, as a blood access device. The action of the antimicrobial at the site of the catheter insertion into the body could make the product a drug. Obviously, this is not what the Congress intended. Congress wanted there to be a clear distinction between drugs and devices, but did not want to create a situation in which products, with intended uses that were primarily device-like, would be treated as a drug.

Thus in 1990, Congress modified the related statutory language. H.R. 3095 was the House bill and S. 3006 was the Senate bill. H.R. 3095 was amended by a conference committee and enacted. The Joint Explanatory Statement of the Committee of the Conference states:

> The Senate amendment but not the House bill describes the general procedures for determining the appropriate component of the FDA to review premarket submissions for products that are comprised of any combination of drug, devices, or biologicals. The conference agreement reflects the Senate provision. [Page 29.]

Thus the report on S. 3006 is pertinent to the issue at hand. It states:

> Section 20 amends section 503 of the act and describes the general procedures for determining the appropriate component of the FDA to review premarket submissions for products that are comprised of any combination of drug, devices, or biologicals. If the Secretary determines that **the** primary mode of action of the combination product is associated with the drugs, devices, or biologicals, then the Secretary shall assign to the organizational unit within FDA, charged with the premarket review of the element associated with the product's primary mode of action, the responsibility to review the premarket submission of the combination product. However, the Secretary will retain the authority to use any FDA resources necessary to ensure adequate premarket review. [Emphasis added, page 43.]

Thus, the Congress intended to have the FDA determine a product's primary mode of action and act accordingly. Congress recognized that an FDA organization other than the one responsible for the review of an application might have the expertise needed to ensure a proper review, but such an event was not meant to change the course of the drug versus device decision. The experts in the other organization were to assist in the review.

In an effort to make all the conforming amendments necessary to implement the modified Section 503, the Senate bill included a modification to both the drug and device definitions. The report states:

> Section 19 alters the drug and device definitions in section 201 of the Act. Language is removed from the drug definition that will permit an approval of a drug/device combination. Changes in the device definition are editorial to make the device definition compatible with the terminology used in section 20. [Page 43.]

The change in the drug definition to which the report refers is the elimination of the phrase "but does not include devices or their components parts or accessories." [See Section 20 of S. 3006.] Thus, this action was not intended to enable the Agency to treat a device as a drug, but to enable the implementation of new Section 503(g).

The change in the device definition to which the report refers is the striking out of "any of its principal" and inserting "its primary" in front of "purposes." Obviously the intent was to have the definition be compatible with Section 503(g). That is, the product is only a drug when its primary intended use is achieved through chemical action within or on the body or through metabolic action. Unfortunately an error was made. The framers neglected to change the last phrase in the device definition, which stated: "...is not dependent upon being metabolized for the achievement of any of its purposes." Thus, the intent of Congress was not met because the last phrase still allowed devices to be treated as drugs. To correct this and other minor language errors in the SMDA, FDA worked with the Congress on the passage of corrective language. As a result, the last phrase was changed to say: "...is not dependent upon being metabolized for the achievement of its primary intended purposes." The term "purposes" remains plural and this could lead to some confusion. Nevertheless, the enactment of Section 503(g), the changes to the drug and device definitions, and the various reports cited above indicate clearly that FDA is to determine if a product is a device or a device-based combination product by determining its primary intended use and then assessing whether this use is accomplished through chemical action within or on the body or through metabolic action. If not, the product is to be regulated as a device or device-based combination product.

## Conclusion

As noted at the beginning of this letter, we ask that you reaffirm that any non-biologic, health care product, or combination product, that does not achieve its primary intended

use through chemical action within or on the body, or through metabolic action, will be regulated as a device or a device-based combination product.

This issue is important to the device industry and, I presume, to the Congress. Thus, I have forwarded a copy of this letter to Ms. Pamela Bailey, President of Advanced Medical Technologies Association, and to Mr. Mark Paoletta, Chief Counsel for the Subcommittee on Oversight and Investigations, House of Representatives. I will, of course, notify them as to the outcome of this matter; not to inform them about whether The Product is treated as a drug or device, but to clarify how such a determination is ultimately made.

Thank you for your attention to this matter.

Sincerely,

Robert L. Sheridan

cc: Mr. Mark Kramer, Office of Combination Devices, FDA
Ms. Suzanne O'Shea, Office of the Ombudsman, FDA
Ms. Pamela Bailey, Advanced Medical Technologies Association
Mr. Mark Paoletta, Subcommittee on Oversight and Investigations, House of Representatives