



August 20, 2004

Division of Dockets Management
5630 Fishers Lane
Rm. 1061
Rockville, MD 20852

Re: Docket No. 2004N-0194

Dear Sir/Madam:

INTRODUCTION

This comment is filed on behalf of the Cook Group, Inc. ("Cook"), a holding company of international corporations engaged in the manufacture of diagnostic and interventional products for radiology, cardiology, urology, gynecology, gastroenterology, wound care, emergency medicine, and surgery. Cook pioneered the development of products used in the Seldinger technique of angiography, and in techniques for interventional radiology and cardiology. Cook products benefit patients by providing doctors with a means of diagnosis and intervention using minimally invasive techniques, as well as by providing innovative products for surgical applications. Cook sells over 15,000 different products which can be purchased in over 60,000 combinations. Many of these devices are used by physicians in the care and treatment of children.

The Cook Group appreciates the opportunity to submit comments to the above-referenced docket in response to the United States Food and Drug Administration's ("FDA's") proposed regulation entitled "Definition of Primary Mode of Action of Combination Products." The proposed regulation defines "mode of action" and "primary mode of action" ("PMOA"), and also includes a decision making algorithm and the requirement that the definitions and algorithm be used in requests for designation under 21 CFR Part 3.

Our general and specific comments identify points of agreement and dispute, and make recommendations in instances where we believe change in the proposal will facilitate the purpose of the regulation, which purportedly is to make the designation process for combination

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products more predictable and transparent, *see* 69 *Fed. Reg.* 25527 (May 7, 2004). Additionally, in our general comments we point out that an underlying agency assumption appears to be that a combination product designation has jurisdictional significance, thus permitting the placement of products within FDA independent of the product's legal status, *i.e.*, as a device, drug or biological product. We believe that the jurisdictional identity of a combination product in the first instance determines the product's assignment to a Center and its pre- and post-market requirements.

GENERAL COMMENTS

Congress clearly understood that a mechanism was needed to end the delay at FDA in assigning combination products to the agency's Centers, and identified the reason for creating section 503(g) of the Federal Food, Drug, and Cosmetic Act (the "FD&C Act" or the "Act") to regulate the designation of combination products by stating, "[t]his provision will provide the Secretary with firm ground rules to direct products promptly to that part of the FDA responsible for reviewing articles that provide the primary mode of action of the combination product." S. Rep. No. 101-953, at 30 (1990). New section 503(g) precisely captured this interest by straightforwardly requiring that after the agency determined the "primary mode of action of the combination product", "the persons charged with the premarket review [of the component providing the primary mode of action of such a product would] have primary jurisdiction." *See* former § 503(g)(1) (West 1999).¹ This approach was not intended to create broad discretion in selecting Centers to regulate products that include a combination of regulated articles; to the contrary, it was intended to create "firm ground rules" to eliminate discretion and require combination product placements based on primary mode of action.

Importantly, as part of the 1990 amendments, Congress also changed the drug and device definitions. These changes, although modest, were made to ensure consistency between new section 503(g) and the Act's definitions. The device definition, as amended in 1976, was intended to not only define a device but to distinguish devices from drugs. *See* H.R. Rep. No. 94-853, at 14 (1976) (stating, "The Committee proposal amends the existing definition of 'device' in section 201(h) of the Act to draw a clear distinction between a 'device' and a 'drug'"). Congress further amended this important definition in 1990 "to make [it] compatible with the terminology used in section 20[, which created the combination product designation rules]." S. Rep. No. 101-953, at 43 (1990). Specifically, Congress struck from the device definition "any of its principal intended purposes" and substituted "its primary intended purposes".² There is no question that "primary mode of action" bore a direct relationship to the

¹ In the Medical Device User Fee and Modernization Act of 2002, Congress amended section 503(g) and changed "persons" to "agency center". *See* § 503(g) (West Supp. 2004).

² The word "purposes" is a carryover from the 1976 legislation. In that context, Congress intended to communicate that a device's identity could change based on its intended use. Congress did not intend to suggest that if a device had a single intended purpose, its jurisdictional status could be influenced by speculation about a second purpose. *See* H.R. Rep. No. 853, 94th Cong., 2d Sess. (1976) 14-15 (stating, "[f]inally, despite the fact that generally the term 'device' is used in the bill to refer to an individual product or to a type or class of products, there may be instances in which a particular device is intended to be used for more than one purpose. In such instances, it is the Committee's intention that each use may, at the Secretary's discretion, be treated as constituting a different device for purposes of classification and other regulation."

limitation in the device definition that a device “does not achieve its primary intended purposes through [chemical or metabolic action within or on the body of man or other animals].” § 201(h) of the Act. In other words, the determination of a combination product’s identity as a device or drug, in the context of its “primary intended purpose[],” is determinative of the product’s primary mode of action.

Contrary to an assumption in the proposed rule that neither the law nor regulations define PMOA, we believe that the term is defined by the classification of a product as a device, drug or biological product. Section 513(g) for devices and section 563 for devices, drugs, and biological products, which require the agency to make product designation decisions,³ as we discuss below, also challenge the notion that the agency cannot in some instances determine primary mode of action. Because under these sections the agency has 60 days by law to make a product jurisdiction decision, *e.g.*, that a product is a device, it is clear that Congress not only believed that FDA could make such decisions, but required the agency to do so after a request from any person. In sum, as a general matter, we believe that the agency must revisit the law and adjust its proposal to effect the efficient, transparent and well-defined process that Congress envisioned.

To this end, on page nine of the comment, we provide a chart that describes the decision tree for a PMOA analysis in most cases. As we discuss below, we believe the agency’s proposed algorithm should be reserved for use in the exceptional cases where two approvals are required. For each basic type of combination product, device-drug, device-biologic, and drug-biologic, the chart first asks “what is the primary intended purpose of the product”, *i.e.*, what is the intended use of the combination product as a whole? After one identifies what the product is intended to do, one then asks how does it do it, *i.e.*, for device-drug or device-biologic combinations, is the product’s mode of action primarily that of a device or of a drug? Specifically, if the product does not primarily achieve its primary intended purpose by chemical or metabolic action, it meets the definition of a device under section 201(h) and must be regulated as such by CDRH. In contrast, it should be regulated as a drug if it achieves its primary intended purpose primarily through chemical or metabolic means.

Under the FD&C Act and for purposes of primary mode of action analysis, biologics are considered drugs. *See infra* pages 4-5. Thus, in the case of a drug-biologic combination one does not have to determine the product’s primary mode of action by determining whether the product is a device or drug under section 201(h) because, by law, the product is a type of drug. *See id.* Instead, one must identify whether the combination’s chemical or metabolic mode of action is primarily a result of the biological constituent. If it is not, the product would be regulated as a drug by CDER. If it primarily works through biological action, it would be regulated as a biologic. Whether CDER or CBER would regulate a combination determined to be a biologic, would be based upon FDA’s administrative product assignment rules for biologics.

³ Section 563 also provides for the agency to classify combination products. However, this classification is for purposes of the section 503(g) designation process only. *See* § 563(a) (stating that “[a] person may submit a request to the Secretary respecting the classification of the product as a . . . combination product *subject to section 503(g)* . . .”). *Id.* (emphasis added). In other words, the agency may inform someone that the person’s product is a combination product subject to the designation process identified in section 503(g). There is no greater significance to a combination product designation under section 563 than clarifying the applicability of section 503(g).

If the combination product's primary intended purpose is therapeutic, under current assignment rules, a biological product likely would be regulated by CDER unless the product is assigned to CBER, e.g., products that are cell-based or vaccines.

SPECIFIC COMMENTS

Mode of Action

The proposed definition of "mode of action" should be more concise and reflect that section 503(g) is part of the FD&C Act and not the Public Health Service Act. Specifically, the definitions should be simplified to directly reflect, without elaboration except where necessary, that a mode of action is dependent upon the definitional status of a constituent part of a combination product as a drug, device or biological product. Currently, although we understand the agency's intent, the regulation almost pre-supposes that a constituent part itself may be a combination of items, e.g., a constituent part "has a device mode of action if . . . , it does not have a biological product mode of action, and it does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and is not dependent upon being metabolized for the achievement of its primary intended purposes." Proposed § 3.2(k)(2). A constituent part cannot itself be a combination product. It should be clear in the mode of action definition that constituent parts are single entity components that are the individual ingredients of a combination product. Additionally, the proposed regulation fails to conceptually distinguish between biological product mode of action and that of a drug or device. We believe a better and simpler way to define "mode of action", although not significantly different than that proposed, would be as follows:

"(k) . . . a constituent part of a combination product is a single entity component that is not itself a combination product, and has— .

(1) a biological mode of action if it has the action of a drug, i.e., chemical or metabolic action within or on the body of man, and acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component, or derivative, allergenic product, or analogous product as those terms are used in section 351(i) of the Public Health Service Act.

(2) a device mode of action if it has the action of a device, i.e., its action does not include chemical or metabolic action within or on the body of man.

(3) a drug mode of action if it has the action of a drug, i.e., chemical or metabolic action within or on the body of man, and it does not act by the means identified in paragraph (1).

In reference to subparagraphs (1)-(3), a constituent part shall retain the identity of its mode of action as biological, device or drug, even if it has an additional incidental biological, device, or drug mode of action."

This approach interprets section 503(g) consistent with Congress's intent in including it in the Act and amending the device and drug definitions in 1990, and FDA's historical approach to biological products as drugs for purposes of the Act. Congress clearly understood that within the meaning of the Act, biological products were drugs. Indeed, the classification of biologics as drugs under the FD&C Act reflects a longstanding agency interpretation of the law⁴ and Congress specifically recognized this interpretation in section 503(g)(1)(A) (stating, "If the Secretary determines that the primary mode of action is that of --- (A) a drug (other than a biological product), the agency center charged with the premarket review of drugs shall have primary jurisdiction, . . ."). The identity of biologics as drugs is also recognized in section 351 of the Public Health Service Act ("PHS Act"). See § 351(j) of the PHS Act (stating that if a biological product has an approved license, it is not required to have an approved new drug application under section 505 of the FD&C Act); see also § 351(g) of the PHS Act (stating that "[n]othing contained in [the PHS Act] shall be construed as affecting, modifying, repealing, or superseding the provisions of the [FD&C Act]"). Effectively, the inclusion in section 503(g) of the reference to the definition of biological product in section 351 of the PHS Act, see section 503(g)(4)(A), was only intended as a means to distinguish between drugs with biological constituents and those that achieve chemical or metabolic effects in non-biological ways.

Because Congress conformed the FD&C Act's definitions and section 503(g) to each other, and because FDA's longstanding interpretation is that biological products are also drugs, defining mode of action in the above recommended manner is consistent with Congress's means of distinguishing between devices and those products that achieve their primary intended purposes through chemical or metabolic action within or on the body of man. Stated another way, by defining biological product in terms of the Public Health Service Act, Congress made sure there was no confusion about what the term meant for purposes of identifying the type of product it was referring to in the context of a combination product designation. However, this statutory reference did not further the primary mode of action analysis for device/biological product combinations under the FD&C Act, which can only be conducted with reference to section 201(h). Significantly, the Public Health Service Act definition of biological product does not address combination products or primary mode of action, and was only important for inclusion in section 503(g) to distinguish between drugs and biologics in the few instances when such products would form a combination product. The above-recommended definitions of mode of action give the Act its fullest effect and permit the determination of primary mode of action in the context Congress set forth in 1990.

Primary Mode of Action

We are concerned that the proposed definition of "primary mode of action" fails to incorporate the concept of "primary intended purposes" of a combination product into its meaning. In other words, the proposed definition, rather than following statutory distinctions between drugs, including biological products, and devices sets out on a new tack, which provides a subjectivity that could ignore the lawful basis for product classification and designation.

⁴ For example, in agency regulations, biologics are subject to current good manufacturing practices for drugs and investigational new drug requirements that permit the introduction of unapproved drugs into interstate commerce.

From May 28, 1976, forward, Congress envisioned products that could have more than one regulated component. The device definition was modified in the “Medical Device Amendments of 1976” specifically to distinguish between products that achieve their primary intended purposes through device mechanisms and those which did so through drug mechanisms. Interestingly, under the act as amended in 1976, a device could have a secondary drug component and legally be a device, yet a product could not legally be a drug if it contained a device, or a device component or part. In 1990, Congress amended the drug definition so that it could contain a device component, thus amending the drug definition to be consistent with the combination product concept and the device definition. As a result, in 1990, Congress intended that combination products would be jurisdictionally classified as a device or drug, including a biological product. In other words, combination products would be devices, drugs or biological products, unless in rare instances a combination product had no primary mode of action, necessitating two jurisdictional designations and two market clearances as a result, *see* S. Rep. No. 101-513, at 31 (1990) (discussing how the maker of a novel drug delivery system would be required to obtain two market clearances, one for the drug and one for the device).⁵ This view was perfectly reasonable because the FD&C Act’s approval and enforcement authorities relate exclusively to drugs and devices,⁶ not combination products.

Although the proposed regulation’s reliance on “*the most important therapeutic action of the combination product*” to determine a product’s primary mode of action⁷ may produce the same result as relying on the product’s jurisdictional status, we are concerned that it will not because of the subjectivity inherent in the proposed concept. Specifically, the statement in the proposal that “[t]he most important therapeutic action is the mode of action expected to make the greatest contribution to the overall therapeutic effects of the combination product” is laden with subjectivity such as what is the “most important” therapeutic action? Does the “therapeutic effect” coincide with the product’s intended purpose? How is the therapeutic effect determined? What is the standard for determining the most important therapeutic action? And what is the greatest contribution to the overall therapeutic effect of a combination product? Each of these questions underscores the fact that the primary mode of action definition selected for the proposed regulation is not statutorily based. We recommend the following, which is simple, statutorily based, and consistent with Congress’s intent to have FDA make product jurisdictional decisions for devices, drugs and biological products:

“(m) *Primary mode of action* is determined by the jurisdictional classification of the combination product as a whole as a device, drug or biological product. To the extent a combination product has components with two distinct modes of action that function independently of each other, or which have no effect in the absence of the other, to produce either a single therapeutic result or multiple therapeutic results, reliance on the

⁵ Congress understood that two distinct market clearances could occur, but likewise understood they could occur within one component of FDA, where appropriate.

⁶ The FD&C Act’s drug misbranding and adulteration authorities are applied to biological products.

⁷ Proposed 21 CFR § 3.2(m)(emphasis added).

algorithm in section 3.4(b) shall determine the agency component with primary jurisdiction over the combination product.”

This approach ensures that combination products will be reviewed by those persons at FDA with the most expertise related to the type of product under consideration. If the combination product is classified as a device, drug or biological product, the Center at FDA principally responsible for regulating such products will have primary responsibility for them. If the product is made up of a drug and a device that do not enhance each other, but instead have independent or complementary roles, those types of products should require two premarket clearances and should be assigned to one Center according to the algorithm. Under either scenario, the public health is well served by ensuring that the FDA assigns such combination products to the Center with the most experience and expertise with such a product.

The Algorithm

We endorse the algorithm and the assignment criteria of proposed section 3.4(b). What we disagree with is the description of when the algorithm should be used. As stated above, when a combination product is composed of constituent parts with two distinct modes of action that function independently, or which have no effect in the absence of the other, to produce a therapeutic result or multiple results, then the algorithm should be used. We are particularly concerned that the “reasonable certainty” criterion for determining a primary mode of action included in the proposed section 3.4(b) creates a very high bar which has the capacity to push a lot of combination products into the algorithm that should be resolved under sections 503(g) and 201(h), thus undermining the “firm rules” Congress sought for combination product designations. Specifically, the reasonable certainty criterion is open to enormous abuse and could effectively increase the agency’s discretion on product designations to a point that the rules under section 503(g) will become exceptions and the algorithm will become the means by which combination products are generally directed to an FDA Center for premarket review and regulation. This result is simply unacceptable because it essentially undermines the law. Accordingly, we propose that the agency strike the first sentence and the first word of the second sentence, *i.e.*, the word “Then”, of proposed section 3.4(b), and in its place, insert the following:

“(b) In some situations, there is no primary mode of action because each constituent of a combination product either works by itself to produce a distinct therapeutic action or each component is dependent on the other to produce any therapeutic action. Under either of these circumstances, . . .”

This result is wholly consistent with Congress’s intent as expressed in “The Safe Medical Devices Act of 1990” and it recognizes that combination products for regulatory purposes are drugs, devices or biological products, or in infrequent circumstances, products that require more than one premarket clearance and postmarket regulation under the separate authorities applicable to the distinct constituents of the combination product. This approach also conforms to Congress’ intent that combination products be regulated consistently and preferably in a single FDA Center.

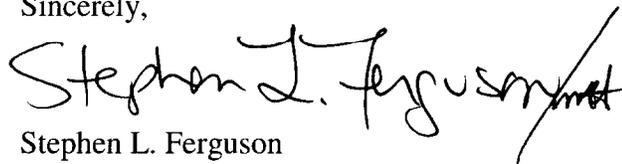
In closing, to be consistent with the Act, we recommend that the agency's proposed amendments to subsections 3.7(c)(2)(ix) and 3.7(c)(3) be revised to read:

“(2)(ix) Description of all known modes of action, and the sponsor's identification of the single mode of action by which the product primarily achieves its primary intended purpose.

(c)(3) The sponsor's recommendation as to which agency component should have primary jurisdiction based on the mode of action by which the product primarily achieves its primary intended purpose. To the extent a combination product has constituent parts with two distinct modes of action that function independently of each other, or which have no effect in the absence of the other, to produce either a single therapeutic result or multiple therapeutic results, the sponsor's recommendation must be based on the algorithm set forth in section 3.4(b), including an assessment of the assignment of other combination products the sponsor wishes FDA to consider during the assignment of its combination product.”⁸

In addition, we believe that the second to last step of the algorithm considering whether there is “an agency component that regulates other combination products that present similar questions of safety and effectiveness with regard to the combination product as a whole” is crucial to ensuring consistent treatment of products. However, this step cannot be implemented effectively and transparently without prompt and full disclosure to the extent allowed by law of all past and future agency jurisdictional decisions. Currently the agency has only three “jurisdictional updates” pertaining to types of products available on its website. To achieve full transparency in the designation process, we recommend that the agency establish and publish written policies and procedures for disclosing individual designation decisions on its website. Finally, we note that the last step of the algorithm that considers “which agency component has the most expertise related to the most significant safety and effectiveness questions presented by the combination product” also introduces subjectivity into the designation process and should be reserved for those products that truly present novel issues to the agency.

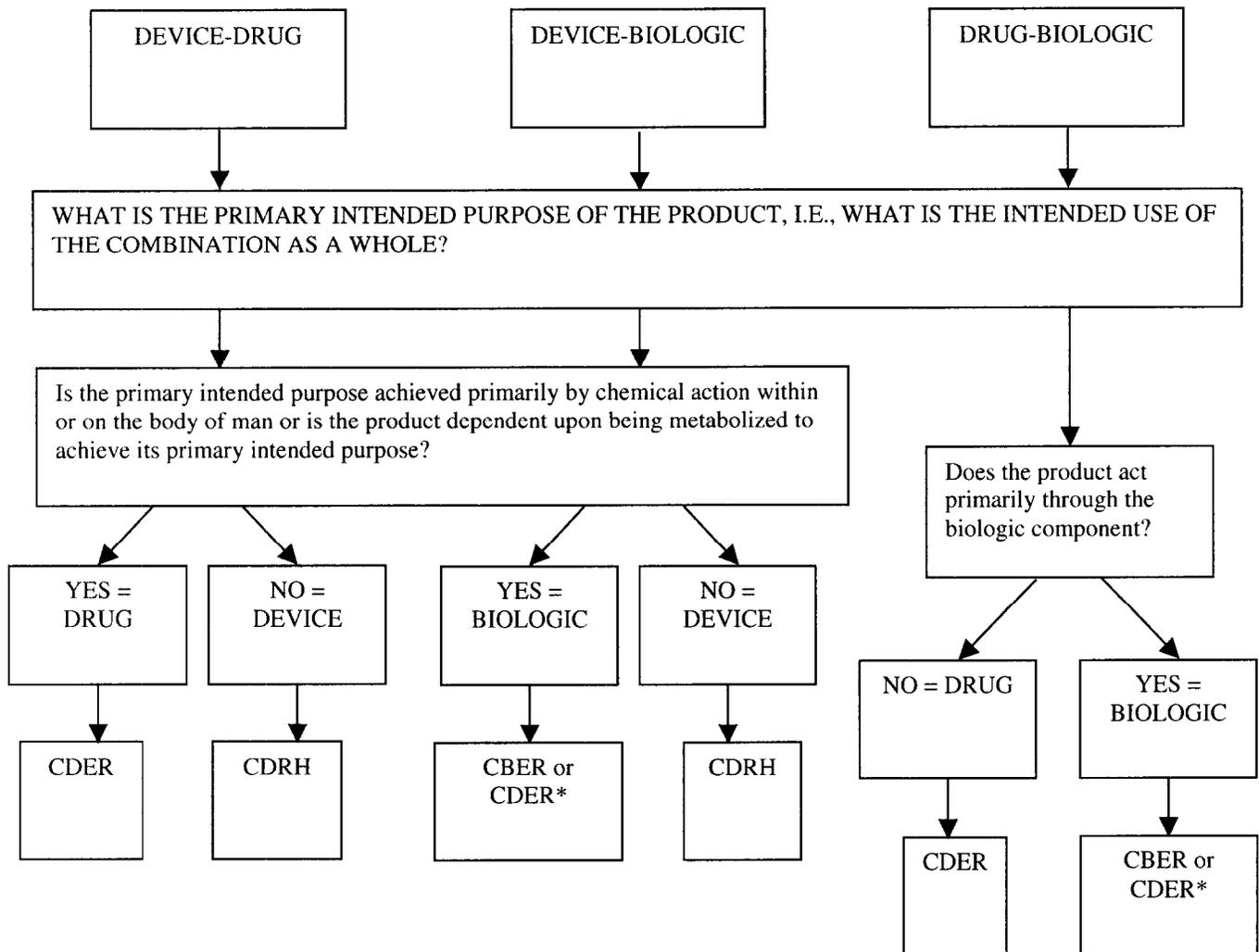
Sincerely,



Stephen L. Ferguson
Executive Vice President and
Chairman of the Board,
Cook Group, Incorporated

⁸ We changed “and an assessment of the assignment of other combination products . . .” in the agency's proposed (c)(3) to “including an assessment of the assignment of other combination products . . .” because the consideration of assignment of other combination products that present similar questions of safety and effectiveness is a step in the algorithm, rather than a separate consideration.

PMOA DECISION TREE



*The assignment of combination products deemed to be biologics under the Act will depend on administrative product assignment rules for biologics implemented by a 2003 agency reorganization that moved many therapeutic biological products to CDER.