July 12, 2018

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

Re: Docket No. FDA-2004-N-0191: Product Jurisdiction

Dear Sir or Madame:

The Advanced Medical Technology Association (“AdvaMed”) appreciates the opportunity to provide comments on the Food and Drug Administration (“FDA” or “Agency”) proposed rule, Product Jurisdiction (“the Product Jurisdiction rule”).

AdvaMed is the world’s largest association representing manufacturers of medical devices, diagnostic products, and medical technology. AdvaMed’s member companies range from the largest to the smallest medical product innovators and manufacturers, with nearly 70 percent of our members generating less than $100 million in annual sales. AdvaMed’s member companies produce innovations that transform health care through earlier disease detection, less invasive procedures, and more effective treatments.

We commend FDA for recognizing the need to update its product jurisdiction regulations to reflect recent legislation and Agency experience. We agree with FDA that this update creates opportunities to streamline the regulations and make them more transparent and efficient. But we are concerned that some of the proposed revisions run counter to the plain language and intent of Section 3038 of the 21st Century Cures Act (“the Cures Act”). The following discussion details these concerns and recommends actions to resolve them.

The Product Jurisdiction rule omits the Cures Act’s restriction against determining primary mode of action based on any chemical action within or on the human body.

The Product Jurisdiction rule defines primary mode of action (“PMOA”) as “the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.” 83 Fed. Reg. 22435 (May 15, 2018), section § 3.2. This definition, however, seems to overlook the Cures Act’s addition of section 503(g)(1)(E) to the Federal Food, Drug, and Cosmetic Act. This provision prohibits FDA from determining that “the primary mode of action is that of a drug or biological product solely because the combination product has any chemical action within or on the human body.” The Cures Act, § 3038(a) (emphasis added).
Through the Cures Act, Congress explicitly directed that a combination product’s primary mode of action shall not be determined to be that of a drug or biologic solely because the product features “any chemical action” in or on the body. This principle reflects Congressional concern that the presence of even minimal chemical action often leads FDA to conclude that a product’s primary mode of action is that of a drug or biologic, rather than a device. Given the importance of this principle to addressing the problem that Congress identified with FDA’s drug-centric classification approach, FDA should affirm in its rulemaking the proposition that it will not make a drug or biologic classification based on any chemical action. Indeed, courts have repeatedly agreed that, in implementing or revising regulations, agencies must account for the underlying “problem” that the regulations – and the statutory provisions underpinning the regulations – are designed to address. See, e.g., Motor Vehicle Mfrs. Assn. v. State Farm Mut., 463 U.S. 29, 43 (1983) (“Normally, an agency rule would be arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, [or] offered an explanation for its decision that runs counter to the evidence before the agency . . . .”) (emphasis added); Michigan v. E.P.A., 135 S. Ct. 2699, 2706 (2015) (“[A]gency action is lawful only if it rests on a consideration of the relevant factors. Although this term leaves agencies with flexibility, an agency may not entirely fail to consider an important aspect of the problem when deciding whether regulation is appropriate.”) (internal citations and quotation marks omitted) (emphasis added); Gray Panthers Advocacy Comm. v. Sullivan, 936 F.2d 1284, 1288 (D.C. Cir. 1991) (“[A]n agency engaged in notice-and-comment rulemaking under section 553 of the APA must explain how the new rules meet the statutory standard. . . . [T]o facilitate judicial review, the agency must discuss, in the concise general statement of the rule's basis and purpose, how it has complied with the applicable strictures in promulgating its new regulations.”) (internal citations and quotation marks omitted) (emphasis added). In this case, the problem is over-inclusive assessment of chemical action as a basis for drug classification. The solution to this problem is to make plain in the amended classification regulations that FDA will not classify products as drugs based solely on “any” chemical action. Thus, we recommend addition of the following language:

In determining the primary mode of action of a combination product, FDA will not determine that the primary mode of action is that of a drug or biological product solely because the combination product has any chemical action within or on the human body.

We acknowledge FDA’s statement in footnote 1 of the Product Jurisdiction Rule preamble that parts of Section 3038 “serve to codify longstanding Agency regulatory interpretations and practices.” 83 Fed. Reg. 22431 (May 15, 2018). But we do not entirely share this view of a longstanding practice of classifications without reference to any chemical action in or on the body. Indeed, in FDA’s draft guidance, “Classification of Products as Drugs and Devices & Additional Product Classification Issues” (“Draft Classification Guidance”), the Agency maintained that “a product that depends, even in part, on chemical action within or on the body of man to achieve any one of its primary intended purposes, would not be a device.” Draft Classification Guidance at pp. 4-5 (emphasis added). The phrase “even in part” applies a stricter standard to classifications than the plain language of Section 201(h), which provides that a product may be a device if it does not achieve its “primary intended purpose” through
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chemical action in or on the body. 21 U.S.C. § 321(h). We understand that the final guidance omitted the “even in part” qualification, but the draft nevertheless suggests that FDA has not always applied the principle that any chemical action in or on the body, on its own, does not exclude a product from device classification. Indeed, the need to clarify this prohibition, and to assure that sponsors may challenge drug or biologic determinations, underpins the development and inclusion of Section 3038 in the Cures Act.

In addition, we suggest that 21 CFR Part 3 be expanded to include the entire decision-making process associated with PMOA, including sponsor challenges of an initial determination. Notably, the Cures Act prescribes the steps that a sponsor should take if it disagrees with FDA’s PMOA determination. In these cases, the sponsor should

[R]equest, and the Secretary shall provide, a substantive rationale to such sponsor that references scientific evidence provided by the sponsor and any other scientific evidence relied upon by the Secretary to support such determination; and

(ii) the sponsor of the combination product may propose one or more studies (which may be nonclinical, clinical, or both) to establish the relevance, if any, of the chemical action in achieving the primary mode of action of such product;
(II) if the sponsor proposes any such studies, the Secretary and the sponsor of such product shall collaborate and seek to reach agreement, within a reasonable time of such proposal, not to exceed 90 calendar days, on the design of such studies; and
(III) if an agreement is reached under subclause (II) and the sponsor conducts one or more of such studies, the Secretary shall consider the data resulting from any such study when reevaluating the determination of the primary mode of action of such product, and unless and until such reevaluation has occurred and the Secretary issues a new determination, the determination of the Secretary under subparagraph (D) shall remain in effect.

These dual mandates – that FDA shall not determine PMOA based solely on chemical action within or on the body, and that sponsors shall have a mechanism to challenge PMOA determinations – should be explicitly incorporated into the proposed regulatory amendments. The language above that we propose to add to the regulation captures the prohibition against determining PMOA based solely on chemical action in or on the body. To clarify sponsors’ right to challenge PMOA determinations, we recommend adding the following language:

If a sponsor of a combination product disagrees with the determination of primary mode of action, then the sponsor may request, and FDA will provide, a substantive rationale that references scientific evidence provided by the sponsor and any other scientific evidence relied upon to support the determination. The sponsor may propose one or more studies (which may be nonclinical, clinical, or both) to establish the relevance, if any, of the chemical action in achieving the primary mode of action of such product, and FDA will
collaborate and seek to reach agreement on the design of such studies. FDA will consider the data resulting from any such study when reevaluating the determination of the primary mode of action of such product.

To permit a meaningful exchange between sponsors and FDA when sponsors challenge PMOA determinations, if a sponsor requests a waiver, FDA should waive the 15-page limit for standard requests for determination. We agree that FDA reviewers should not sift through voluminous documents to make standard classification decisions. But challenging a PMOA determination is different: sponsors bear the burden of proof in these cases, which they must have the chance to meet through detailed and complete presentation of their positions. To forestall compelling arguments in the name of brevity serves neither FDA nor the public.

We also note that FDA has failed to incorporate in guidance the prohibition against determining PMOA based on any chemical action and the mechanism for sponsors to challenge PMOA determinations. FDA issued its final guidance, “Classification of Products as Drugs and Devices & Additional Product Classification Issues,” about nine months after passage of the Cures Act. Despite clear and prescriptive statutory language, this guidance does not reference either of the above principles. We believe that this omission departs from the stated intent of Section 3038 and we recommend that FDA revise the guidance to clarify: (1) that it will not determine PMOA based solely on any chemical action in or on the body; and (2) that sponsors may pursue the process described in Section 3038 to challenge PMOA determinations.

**FDA’s redefinition of “mode of action” is overly restrictive and may lead to the mischaracterization of products.**

We respectfully disagree with the proposed changes to the definition of “mode of action,” and we are concerned that this change might lead to the misclassification of devices as drugs or biologics. The current regulation defines mode of action as “the means by which a product achieves an intended therapeutic effect or action. . . . [C]ombination products will typically have more than one identifiable mode of action.” 21 CFR § 3.3(k) (emphasis added). By contrast, the Product Jurisdiction rule proposes to state that “[e]ach constituent part of a combination product has one such type of mode of action.” 83 Fed. Reg. 22435 (May 15, 2018), section § 3.2. (emphasis added).

Under section 201(h) of the Food, Drug, and Cosmetic Act, a device is a product that “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 upon being metabolized for the achievement of its primary intended purpose.” 21 U.S.C. § 321(h). Under the proposed definition of “mode of action,” a product meeting the definition of a device under section 201(h) could nevertheless be improperly characterized as a drug or biologic simply because it includes some chemical action. That is inconsistent with the device definition and Congress’s direction in section 3038 of the Cures Act that FDA shall not characterize a combination product as a drug or biologic based on any chemical action. Thus, a combination product may include as a constituent part a device with multiple modes of action – each achieved through different means – one of which is through chemical action that is not the device’s “primary intended
purpose.” To characterize this constituent part as a drug based only on the presence of chemical action is wrong. To avoid this result, AdvaMed recommends striking the proposed language and maintaining the existing language.

**FDA should incorporate by regulation the Cures Act’s framework for combining and separating combination product applications.**

The Cures Act states that combination products shall be reviewed under a single application whenever appropriate, and that sponsors may submit separate applications for the constituent parts of a combination product unless FDA determines that a single application is necessary (see 21 U.S.C. 353(g)(1)(B) and (6)). FDA indicates in the preamble to the Product Jurisdiction rule that

§ 3.4(c) states in part that the Agency can require in appropriate cases that constituent parts of a combination product be reviewed under separate applications. Accordingly, to avoid confusion . . . the proposed rule would remove this language at § 3.4(c). FDA intends to issue guidance regarding implementation of the new statutory provisions as needed given Agency experience with implementing them.

83 Fed. Reg. 22431 May 15, 2018 (footnote omitted). The best mechanism to avoid confusion is to amend the regulation to specifically adopt the review language included in the Cures Act. Excising contradictory language with the promise of guidance at a later date leaves a gap that will increase, not avoid, confusion. Of course, we welcome guidance that supplements regulatory language should FDA decide that guidance will help stakeholders understand Agency intent and expectations.

**FDA should clarify that Section 3.5 in the Product Jurisdiction rule applies only in cases of uncertainty or disagreement.**

Sections 3.1 and 3.3 in the Product Jurisdiction rule define the rule’s purpose and scope as instances in which “product classification or assignment is unclear or in dispute.” 83 Fed. Reg. 22434, 22435 (May 15, 2018). FDA should likewise clarify that sponsors should request designation under section 3.5 of the Product Jurisdiction rule only when product classification or assignment is unclear or in dispute. This clarification will avoid the inefficiency of a sponsor requesting designation when the nature of a product is well-established and does not require an individualized determination.
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AdvaMed thanks FDA for its consideration of these comments. Please do not hesitate to contact me at 202-434-7243 or ssilverman@advamed.org if you have any questions.

Respectfully Submitted,

/s/
Steve Silverman
Vice President
Technology & Regulatory Affairs
AdvaMed