



September 15, 2011

VIA ELECTRONIC SUBMISSION

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

Re: Draft Guidance for Industry and Food and Drug Administration Staff:
Classification of Products as Drugs and Devices and Additional Product
Classification Issues; Docket No. FDA-2011-D-0429

Dear Sir or Madam:

The Combination Products Coalition (“CPC”) is pleased to offer its comments on the Draft Guidance for Industry and FDA Staff, *Classification of Products as Drugs and Devices and Additional Product Classification Issues* (“Guidance”).

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products area. One of the principal goals of our organization is to work with the Agency on issues affecting combination products, in order to advance our common missions of providing the best possible health care for patients. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

GENERAL COMMENTS

First, the CPC would like to commend the Agency on providing clear guidance regarding the Agency’s general interpretations of the definition of a device. For example, the Guidance explains key terms in the statutory definition of device, such as “similar or related article” and “does not achieve its primary intended purposes through chemical action within or on the body of man or other animals.”

With respect to combination products specifically, although the Guidance does not directly address combination products, the Guidance affects combination product manufacturers. In this regard, the CPC is concerned that the application of this Guidance by the Office of Combination Products (“OCP”) may prevent the OCP from meeting its statutorily-mandated mission of ensuring “the consistency and appropriateness of postmarket regulation of like

products subject to the same statutory requirements.”¹ The Guidance itself acknowledges that its application may cause the same product or combination product constituent part to have two different classifications, at least for a short period of time.² In addition to this specific statutory mission, under principles of administrative law, an agency’s adherence to precedent mitigates the risk of a judicial reversal based on a finding that the Agency’s action was “arbitrary and capricious.”³ And finally, the Federal Food Drug & Cosmetic Act requires that classifications obtained through the Request for Determination (“RFD”) process not be changed absent public health reasons based on scientific evidence – in other words, scientific evidence, standing alone, is not enough to compel a change.⁴

In addition to legal reasons, following precedent has important practical benefits. Precedent leads to predictability and fosters compliance, which makes for good governance.

Making Agency decisions publicly available also supports the Agency’s Transparency Initiative and the goals and mission of the FDA Transparency Task Force. As the CPC recently described in our recent letter to Dr. Hamburg and the FDA Transparency Task Force, CPC believes it is imperative for the OCP to ensure transparency in its decision-making. This transparency is important to support the Transparency Initiative broadly, and it is especially important in an area such as combination products, where policy and regulation are still developing.

Importantly, our specific comments below pertain primarily to drug and device issues. In this regard, similar guidance on the boundaries of the definitions of biological products and combination products specifically would be tremendously helpful. Guidance on the definition of biological products is particularly relevant in light of the definition for biologics in the Biologics Price Competition and Innovation Act of 2009.

With these general comments in mind, the purpose of our specific comments below is to identify particular areas in which the Guidance needs clarification or revision to enable the OCP to ensure transparency and to satisfy its statutory charter of ensuring consistent and appropriate regulation of similar products through consistent classification decisions. To that end, we offer the following specific comments.

¹ 21 U.S.C. § 353(g)(4)(D).

² “FDA can classify the product or constituent part presented in the RFD in accordance with current scientific understanding and applicable statutory definitions, notwithstanding the fact that such determination has led to a classification that is different from the previous classification of the same product or constituent part.” Guidance FN 10.

³ See 5 U.S.C. § 706(2)(a).

⁴ 21 U.S.C. § 360bbb–2 (an exception to this requirement is if the person gives consent for the classification to be changed).

SPECIFIC COMMENTS

1. Status of Intercenter Agreements.

The *Federal Register* notice announcing the availability of the Guidance states that the Guidance “presents the Agency’s current thinking on the status of published intercenter agreements, current regulations establishing classifications, and classifications the Agency has otherwise previously made for specific products.”⁵ However, we believe there is opportunity for the Guidance to provide greater insight into the Agency’s current thinking regarding the status of the intercenter agreements.

More specifically, the Guidance reiterates that the intercenter agreements constitute nonbinding determinations; that “they should not be independently relied upon as the Agency’s most current, complete jurisdictional statements”;⁶ and that the Agency is currently evaluating whether to modify or replace the agreements. The Guidance goes on to state that certain classification determinations within the intercenter agreements are superseded to the extent those determinations are inconsistent with the Guidance. However, the Guidance does not specify the superseded classification determinations and does not provide other guidance as to what classification determinations are no longer valid. Additional guidance in these areas is important to ensure both Agency staff and industry understand and appreciate possible impacted product classifications.

Importantly, this ambiguity concerning the intercenter agreements has been ongoing in other contexts as well. In particular, the Medical Device User Fee and Modernization Act (MDUFMA), passed in October 2002, included a provision requiring the “Secretary..., acting through the [OCP], to review each agreement, ... that is specific to the assignment of combination products to agency centers and to determine whether the agreement” is consistent with the statutory charter of the OCP.⁷ Consistent with that commitment, nearly five years ago, the Agency publicly acknowledged that the intercenter agreements should not be independently relied upon as the Agency’s most current, complete jurisdictional statements.⁸ At that time, the Agency concluded that transparency to its jurisdictional decision-making would be best achieved *not* by modifying or updating the intercenter agreements, but rather by other means, including “frequently issuing jurisdictional information ... as that information becomes available.”⁹ However, since this statement was made, FDA has published only two redacted RFD decision letters and none since January 2007.¹⁰

The CPC urges FDA to remedy this ambiguity. We understand that the status of the various sections of the intercenter agreements is not binary, and they cannot be fixed merely by pruning certain sections. However, manufacturers must be able to understand what parts of the

⁵ 76 Fed. Reg. 36,133, 36,134 (June 21, 2011).

⁶ Guidance at 6, citing 17 Fed. Reg. 56,988 (September 28, 2006).

⁷ 21 U.S.C. § 353(g)(4)(F).

⁸ 71 Fed. Reg. 56,988 (Sept. 28, 2006).

⁹ *Id.* at 56,990.

¹⁰ See FDA Redacted Decision Letters page at

<http://www.fda.gov/CombinationProducts/JurisdictionalInformation/RFDJurisdictionalDecisions/RedactedDecisionLetters/default.htm>

agreements remain viable and what parts have been overcome by scientific facts and events. For the reasons more fully discussed in next section, manufacturers must be able to understand, from a very early stage in the development process, whether a product is likely to be considered a drug, device, or biological product. Therefore, we urge the FDA to update the current intercenter agreements or draft new intercenter agreements or other publicly-available documents that reflect the Agency's current thinking. We are particularly interested in any modifications to the CDRH-CBER agreements, as Agency presentations as recently as three years ago indicated that the vast majority of determinations in that agreement were still current.

Further, if the Guidance is applied as written – cautioning against relying too heavily on previous Agency classification decisions – the number of RFDs submitted to the Agency may well increase, as manufacturers seek an understanding of their product classification. An increase in RFDs will further strain the Agency's and the OCP's limited resources. Several important combination product policy issues are now percolating within the OCP and industry, and issuing this Guidance in its current form could result in RFDs consuming even more Agency resources, thereby hampering OCP's ability to advance policy and hindering the OCP's informal interactions with industry on policy and other regulatory issues. Transparency in the Agency's current thinking on product classification could avoid these potential roadblocks.

In summary, to the extent the Agency has concluded that certain previous decisions can no longer be relied upon, FDA should proactively inform manufacturers and provide them with the basis for the decision and an opportunity to respond. In particular, the Agency should indicate which sections of the intercenter agreements have been superseded by either this Guidance or other Agency determinations or are no longer valid as written. We realize that in many cases, whether a section or product category is superseded, or otherwise no longer valid as written, depends on certain factors. In these cases, the Agency should supplement the intercenter agreements with an explanation of these factors or rewrite those sections of the agreements. Additionally, we ask that FDA make available all RFD decisions and recommence providing redacted RFD decision letters, jurisdictional determinations, and jurisdictional updates so that manufacturers are informed regarding FDA's current thinking about the classification of certain products.

2. Classification of Products When Existing Classification is Established by Regulation

If a regulation establishes the classification of a product, the Guidance proposes to continue to apply the existing classification until or unless the Agency revises the regulation. Thus, in response to an RFD, the Agency would classify the product or constituent part in accordance with the regulation, if the product or constituent part is within the scope of that regulation. If the Agency determines that it is appropriate to change the classification, it would do so through notice and comment rulemaking. We agree with the Agency that this is the appropriate process for this situation.

3. Classification of Products When Existing Classification is Not Established by Regulation.

The Guidance proposes to allow a manufacturer's classification recommendation to stand – without intervention by the Agency – in instances where the Agency concludes that current

scientific understanding may lead to a different product classification than previously applied by the Agency. The Guidance acknowledges that such an outcome may occur when the Agency plans to transfer the classification of such products at a later date.

We understand that the Agency intended this proposal to benefit manufacturers, in that the Agency will allow a manufacturer's classification recommendation to stand even though the Agency believes that current scientific understanding may lead to a different conclusion. We further understand that once the Agency determines that previous classification determinations are no longer supported by current scientific understanding and determinations of similar products will result in different classifications, FDA will need to take steps to ensure such products are subject to evenhanded regulation. However, the proposal contained in the Guidance may have significant negative impacts on the manufacturer, as there are a multitude of regulatory and practical implications that depend on a product's classification.

As the Agency is well aware, there are different regulatory requirements with which a manufacturer must comply depending on a product's classification as a drug or device. Although some of these regulations are similar or may be applied on a going-forward basis, certain requirements must be implemented during the development process. These include, for example, device design controls and clinical trial requirements for various product types. Another major issue with moving products from device to drug status relates to the method of product sterilization, and especially radiation sterilization. This method is commonly used for devices, and devices that are radiation-sterilized can usually go to market via the 510(k) process. However, if used on a drug, it results in the drug being a new drug. Further, changing regulatory schemes mid-stream would cause the manufacturer to incur significant resource and financial consequences. Beyond a quality systems impact, the classification of a product may affect whether the product is eligible for patent term restorations and certain non-patent exclusivity provisions.

In addition to the FDA regulatory and economic impact, other important issues may be affected should FDA change a product's classification *ex post facto*. For instance, how a product is reimbursed by public and private health insurance payors depends upon a product's classification, such that a change in classification likely will directly affect how the product is covered and paid for by public and private payors. The process associated with complying with a new coverage scheme due to a change in the product's classification is complex and could result in reducing or eliminating the public's access to a product.

For these reasons, if FDA believes, based on its current scientific understanding, that the classification of a category of products should be changed, FDA should promptly inform the public about its intent to reclassify the group of products and solicit comment through an open and public process. The process should be expedited so that new market entrants are not prejudiced. Until the classification is changed, the Agency should adhere to established precedent.

Further, with regard to changing precedent, the Guidance observes:

“In instances where an RFD determination has led to a new classification that is different from the previous classification of

the same product or constituent part, it is FDA's intention to initiate an administrative process, consistent with principles of transparency and applicable legal requirements, to resolve these differences in classification."¹¹

Although we are pleased that the Agency recognizes a change in classification will be made transparently and in accordance with legal requirements, we believe the Guidance should go beyond this general statement. More specifically, a change to an existing precedent should not be made until the Agency concludes, after public input, that: a change in scientific understanding sufficient to result in a different classification has occurred *and* the public health is not being served by the current regulatory scheme.¹² This conclusion should not be made until the Agency has solicited and received public input through a clear, timely, and meaningful process. The Guidance also should provide a framework under which FDA will evaluate whether a sufficient change in scientific understanding has occurred. This framework should include specific scientific factors to be evaluated by the Agency.

Of course, if a product is truly distinguishable from a category of products and precedent (for example, based upon the product's intended use, technological characteristics, mode of action(s), and the like), the Agency may classify the product accordingly. However, the Agency should publish the classification determination and its rationale so that the public understands the basis for the Agency's decision.

For example, if the Agency concludes, after evaluating specified scientific factors, that available scientific evidence and protection of the public health warrant reclassification, the Agency should provide notice and solicit comment on the potential reclassification and its scientific basis. During the period of notice and comment, which should be expedited so as not to prejudice new market entrants, the Agency should adhere to established precedent. The Agency should not proceed to reclassification until the Agency has solicited and received public input through a clear, timely, and meaningful administrative process.

4. Definition of Device and Relationship to Primary Mode of Action

The Guidance clearly states that "if a product is shown to meet both the drug and device definitions, the Agency generally intends to classify the product as a device." Additionally, "if a product meets the drug definition but there is uncertainty regarding whether it also meets the definition of a device, the Agency generally intends to classify the product as a drug." However, the Guidance does not discuss the impact of these definitional conventions on determining the Primary Mode of Action ("PMOA") for a combination product. For example, consider a situation in which a product has both drug and device components, satisfies both definitions, and is considered a combination product under 21 C.F.R. § 3.2(e). Assume that under 21 C.F.R. 3.2(m), the product's PMOA is that of a drug, and CDER has primary jurisdiction over the product.

¹¹ Guidance, at footnote 10.

¹² This proposal is consistent with FDA's requirements regarding the legal standard for changing a classification determination, which requires a public health reason in addition to scientific evidence. 21 U.S.C. § 360bbb-2.

In this instance, would the Agency override the general principle that a product meeting both drug and device definitions is classified as a device? Or, would the product be classified a device that is regulated by CDER instead of CDRH? Although we are pleased that the Guidance provides clear statements regarding the Agency's general interpretation of the definition of a device, we believe the next iteration of the Guidance should address possible downstream impacts of these definitions.

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We are pleased that the Agency has issued the Guidance and is seeking to provide additional information to industry regarding its current thinking regarding product classification. However, we believe the Guidance lacks specific guidance that would be tremendously useful to FDA staff and the industry. Therefore, we urge the Agency to carefully consider stakeholder comments as it develops the final Guidance. We are happy to help in any way we can.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is fluid and cursive, with a prominent initial "B" and "M".

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