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AdvaMed
Advanced Medical Technology Association

AdvaMed's Written Testimony at FDA Public Hearing: on FDA Regulation of Combination Products

by
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My name is Pat Shrader -- I am Corporate Vice President, Regulatory Affairs and Compliance, at Becton Dickinson -- but I am here today as the member company spokesperson on behalf of Advanced Medical Technology Association, more commonly known as "AdvaMed." AdvaMed is the largest medical technology association in the world, representing more than 1,000 innovators and manufacturers of medical devices. One of AdvaMed's principal roles is to support laws and policies that foster innovation and bring safe and effective technologies -- including device combination technologies -- expeditiously to market.

In its October 28 Federal Register Notice, the Agency raised a number of questions to help frame the discussion on steps needed to refine and improve the regulation of combination products. These questions will be the subject of detailed written responses by AdvaMed, today, we intend to summarize the principal comments and recommendations received from member companies on these important issues.

[Question 1: What types of guiding scientific and policy principles should apply to rewriting the Intercenter Agreements?]

The first of your questions asks for guiding scientific and policy principles that should be factored in to FDA's ongoing efforts to rewrite its Intercenter Agreements. In March of this year, AdvaMed -- along with PhRMA and BIO -- authored and submitted to the Agency several general guiding principles for combination reviews. Since that time, as the Agency is aware, there have been a number of significant developments -- including new amendments to our combination law, and last summer's Part 15 hearing. These developments have further directed and refined, both our understanding and our views on appropriate combination product principles and procedures.

We ask therefore, that the March document be referenced only with respect to certain core themes -- for example, the now statutorily-recognized need for prompt and efficient review of combinations; the need for combinations involving devices to have full use of FDAMA mechanisms to facilitate reviews and foster innovation; and the need for improved and more standardized Intercenter Agreements.

Along with these core themes, however, other recommendations, reflective of more recent developments, should also be considered. These other recommendations will be discussed in the context of responding to the remaining six questions identified in the Federal Register Notice.

[Question 2: What factors should FDA consider in determining the primary mode of action of combinations? If primary mode of action is uncertain, what other factors should come to bear? Is there a hierarchy for these other factors?]

FDA's next question relates to "primary mode of action." The Agency has asked what factors it should consider in determining the "primary mode of action" of combination products. AdvaMed, as you know, has addressed this issue in its presentation at the recent

public hearing in June on combination products containing live cellular components, and in its August 20, 2002 follow-up letter to the Chief Counsel on that same issue.[1/]

As we have conveyed on prior occasions, we believe, interpretive instructions on primary mode of action, already exist -- and are clear -- from the law itself and from FDA's consistent application of its law over many years. Over the last decade, AdvaMed's member companies have come to rely, and build their combination businesses around, two fundamental interpretational standards:

- first, that FDA would look to the combined product --- that is, the product as a whole (and not the relative contribution of each constituent component, as has recently been suggested) -- to assess the primary mode of action; and

- second, that "mode of action" would be determined based on the primary intended function of the combined product.

A principal theme of the CDRH-CDER Intercenter Agreement, as you know, provides that products which have primarily a structural, physical, repair, or reconstruction purpose, should be regulated as devices. From the Intercenter Agreements, from our RFD decisions, and from informal Center assignments over the years, there has emerged a long and varied list of combination products granted primary device status based on the intended function of the composite product. Examples include: drug-eluting stents, antibiotic-filled cement and spinal fusion products containing biomaterials -- all of which serve primarily a structural function; condoms with contraceptive agents, and dental prophylaxis pastes with drug components -- which serve primarily a physical function; and dressings with antimicrobial agents and tissue-engineered wound repair products --which serve primarily a repair/reconstruction function. These are just a small, representative sampling of the many combinations designated devices over the last decade based on an assessment of two essential factors: (1) an assessment of the primary function of the product; and (2) an analysis oriented to the composite product, rather than to detailed evaluation of the relative contributions of each constituent component.

These two interpretive factors -- consistently used, and long in place -- have served both the Agency and industry well. They have fostered innovation on the one hand, and have protected and preserved public health on the other. Innovation has been fostered because of the legal and policy initiatives that are uniquely available under our device premarket review structure. From the public health perspective, we have had over a decade of combination assignments to CDRH, and, to our knowledge, not a single postmarket safety issue has arisen as a result of those assignments.

Companies with combination products regulated as devices based on these two interpretive factors -- primary intended function and composite product -- have oriented their operations around this historical system for classification. Any alteration of their products' status by virtue of new interpretive factors, potentially could change their entire structure and

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1/ See Attachments.

framework for doing business. Given these substantial and potentially severe consequences, AdvaMed believes that formal notice-and-comment processes are legally required if FDA is interested in further defining or clarifying the primary mode of action standard.[2/]

We were gratified to hear from the Agency just last week, in an educational forum concerning MDUFAMA, that any proposed modifications to the historical "primary mode of action" standard, would in fact undergo formal notice-and-comment rulemaking. We agree with the Agency that these issues are too large and important, not to be debated fully and fairly on the record.

As a related question, the Agency has asked what factors should be considered in assigning primary jurisdiction, in instances where the "primary mode of action" of a combination cannot be, or is not easily, determined. Two factors in particular warrant discussion.

As AdvaMed previously has stated, one important equitable factor is whether the same product is already approved or cleared by a particular Center for a different use. Consistency of regulation with respect to product development strategies, and premarket development and testing programs, is important to all companies, large and small. Development and maintenance of multiple premarket review systems for the same core technology, requires a substantial investment of resources, time, and personnel, that will hinder future product development for many companies, and could be so burdensome as to destroy core businesses for others.

The theme of fostering technologies and public health advancements also should be considered. Many, many combinations -- currently regulated as devices -- represent important improvements in patient care. These products have benefited from early collaboration meetings, 100-day meetings, and modular reviews (mechanisms available for every Class III product); least burdensome review principles; and humanitarian device exemption initiatives -- all unique to the device premarket review structure. Since CDRH jurisdiction over combinations has a demonstrated effective review history, in those instances where "primary mode of action" is otherwise unclear, and companies believe that a device assignment would serve to foster and advance their technologies, deference should be given to this important principle.

[Question 3: What general scientific and policy principles should be used in selecting premarket regulatory authority for combinations? Is one set of regulatory authorities more suitable than another for regulating combinations?]

2/ The new legislation provides certain specified procedures for revising agreements, guidances, and practices, but those specified procedures are to be used in the context of ensuring consistency with the requirements of new Subsection 503(g)(4). "Primary mode of action" authority is separately addressed under Section 503(g)(1). Consequently, Subsection 503(g)(4) has no relation to, and does nothing to alter, FDA's notice-and-comment requirements for further defining or clarifying "primary mode of action."

On premarket review issues, FDA has asked what scientific and policy principles should be followed in selecting premarket review authorities for combination products. In its preamble leading up to this question, the Notice observes that, while the Act requires that "primary mode of action" must determine the appropriate Center for review, it does not address which authorities should be used to review the combination product. This statement suggests that there might be flexibility in mixing and matching premarket authorities for combination products. If this is the case, AdvaMed respectfully disagrees for several reasons.

First, Congress has now sent the Agency a clear message that use of premarket device authority by other Centers must be studied. Under Section 205 of MDUFAMA, Congress recognized the premarket concerns of our industry, and required that the Agency prepare a report on the timeliness and effectiveness of device premarket reviews by Centers other than CDRH. Industry concerns with this issue were further affirmed just recently, when the Agency published a self-assessment report on combinations in October. In that report, the Agency offered the following example of other Centers' perspective on device premarket review laws:

> [The Report states that] "[s]ome CBER and CDER participants mistakenly suggest that CDRH does not require effectiveness data, and that the PMA process [is] required only for the first device of a kind ([that is,] the second of a kind could be regulated under the 510(k) process)."

As you will appreciate, these types of comments raise important questions concerning use of device authorities by Centers other than CDRH.

Moreover, in contrast to single-entity products, our combination laws are very clear on the issue of premarket authority. In contrast to single-entity products, the statute states that, if the primary mode of action is that of a device, "the persons charged with premarket review of devices shall have primary jurisdiction."[3/] Consequently, if a combination product is deemed a device, such that device premarket authorities apply, it must by law be assigned to CDRH. No flexibility is afforded the Agency on this issue.

[Question 4: Recognizing the need to ensure product safety and effectiveness, what criteria should be employed to determine whether a single application or separate applications would be most appropriate for combinations? Should the need to apply a mixed regulatory postmarket approach influence whether one application or two are more appropriate?]

The Agency next asks what criteria should be employed to determine whether a single application or separate applications would be most appropriate for combinations. As reflected in the Federal Register, our member companies see the advantages and disadvantages of separate applications in different ways -- at different times -- depending

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3/ Section 503(g)(1)(B) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 353(g)(1)(B).

upon the specific regulatory, factual, and business circumstances presented by their particular combination. We believe, however, that these differing views may be fully reconciled, by distinguishing required separate filings, from separate filings that may be at the option of the sponsor. Several specific recommendations highlight and explain how this distinction would be implemented.

1. First, in order to avoid redundant reviews and excessive regulation, only one filing should be required in the vast majority of cases. Indeed, we believe that, as the consultative process continues to be regularized, improved, and held accountable, there should be fewer and fewer mandated separate applications.

2. There are certain select circumstances, however, where a company at its option might see a separate filing as useful for regulatory or business/marketing reasons. Factors include: a) where two different companies -- for example, a drug company and a device company -- are involved in the manufacture of combination components; b) where components are expected to have separate distribution and use/reuse patterns; and/or c) where primary jurisdiction for the combination has been given to a Center other than CDRH, and the device component is capable of being separately defined and reviewed. Examples include: drug delivery devices, infusion catheters, nebulizers, jet injectors, insulin pens, and laser activated drug delivery systems. In these circumstances, AdvaMed believes that separate filings may be appropriate. The key to this recommendation, however, is that the option of dual filings is left up to the sponsor.

Related to this topic, the Agency also has asked whether the need to apply a mixture of different postmarket approaches, should influence the issue of one application or two. We believe the answer to this question is much like our proposed general approach to dual submissions. That is, a mixture of postmarket authority should not trigger a requirement for more than one application, but some companies, at their option, may regard this as an appropriate contributing reason to request dual submissions.

Question 5: What scientific and policy principles should be followed in determining the appropriate manufacturing and quality system regulatory authorities? In determining the appropriate adverse event reporting authorities?

The Agency's next series of questions address postmarket controls, and ask what scientific and policy principles should determine the appropriate manufacturing and adverse event reporting requirements for combinations. As the Agency is aware, before any science and policy principles are considered, legal principles must come to bear. MDUFAMA mandates that the Agency "ensure the consistency and appropriateness of postmarket regulation of like products subject to the same statutory requirements." In implementing this new law, AdvaMed believes that appropriateness should first and foremost guide postmarket decisions, and that consistency of like products should then follow.

We also believe that the concept of "like products" should be interpreted narrowly, to ensure that manufacture and postmarket reporting decisions are in fact appropriate for each and every specific category of combinations. We believe, for example, that drug-eluting stents and antibiotic-filled cement, are not "like products" for purpose of this analysis. (Their outcomes may or may not be the same; the point is, that the analysis should proceed separately.) We also believe that delivery systems used to augment specific drug therapies will have many subcategories of "like products," each requiring separate evaluation concerning appropriate postmarket approaches. We do not come today prepared to provide specific category-by-category recommendations on these issues; we simply ask that these issues be reviewed on a narrow "like product" basis.

In contrast to FDA's statutory constraint in selecting premarket authorities for combinations, there is no similar constraint for selecting postmarket obligations.[4/] Consequently, we believe that "appropriateness" should address, not simply product types, but also a variety of other factual, equitable, and policy considerations. For example:

- The proposed marketing structure for a combination -- that is, whether the two components of a combination will be sold by different entities and have different distribution and use/reuse schemes -- may be considered in assigning postmarket obligations.

- Similarly, equitable considerations, such as the quality systems and post-market reporting reviews already in place at a sponsoring entity, should be factored in -- not as the most important determinant, but as one that may help sway, when decisions on appropriate postmarket requirements could go either way.

- So too should policy issues come to bear --- for example, there are certain legal requirements that are unique to devices -- design controls in QSRs and malfunctions in MDRs -- and application of these authorities may be useful in defining a single or hybrid postmarket regulatory regime.

The framework for determining appropriateness should be flexible enough to consider all of these various factors, but overarching any decision, should be the avoidance of redundancies and over-regulation.

Finally, the specific "rules of the game" for quality systems and adverse event reporting (and, for that matter, promotional and other compliance systems), should be made very early on for companies -- not simply for those that have sought RFDs, but also for those that have pursued more informal Center assignments -- so that firms can begin to build, and rely on a defined set of postmarket requirements. Similarly, these obligations should be documented,

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4/ Section 503(g)(2) of the FFDCA, 21 U.S.C. § 353(g)(2) (speaking only to premarket authorities, by stating that, "[i]f . . . the primary mode of action is that of . . . a device, the persons charged with premarket review of devices shall have primary jurisdiction") (emphasis added).

not simply for the sponsor, but for Agency personnel as well, to avoid the confusion that a number of our members have experienced.

[Question 6: Other comments concerning the regulation of combination products.]

Finally, with respect to your call for other comments, we offer some points on the proposed structure and function of the new Office of Combination Products. As the Agency is aware, the concept of enhanced authority, was an essential theme advanced by AdvaMed in discussions leading up to the new combination amendments. We believe, as FDA finalizes its plans for establishing this important Office, and ensuring its full authority, that it will provide the Office with clear, direct, and regular access to the Commissioner. We also believe that this Office must be well staffed and sufficiently expert, to meaningfully review the diverse and complex scientific/clinical issues that so often confront combination technologies.

And with those final recommendations, AdvaMed thanks the Panel for its time today and for its serious consideration of our comments.

Attachments