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VICE PRESIDENT  
SCIENCE POLICY AND TECHNICAL AFFAIRS



2004D-0182

July 2, 2004

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

Re: Draft Guidance for Industry on Combination Products, Timeliness of Premarket Reviews, Dispute Resolution [Docket No. 2004D-0182, 69 *Federal Register*, 24653 (May 4, 2004)]

Dear Madam/Sir:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than \$30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

The members of PhRMA fully support the implementation of the Food and Drug Administration's (FDA) Office of Combination Products and the activities that the office is undertaking to clarify the regulation of combination products. We appreciate the opportunity to provide comments on the draft document "Combination Products, Timeliness of Premarket Reviews, Dispute Resolution Guidance."

General Comments:

The language of the statute establishing the Office of Combination Products (OCP) charged the new office with "coordinating reviews involving more than one agency center." 21 U.S.C. §353(g)(4)(C)(i). We view the formation of the OCP as an important opportunity to improve communication between the applicant and the FDA Centers to resolve disputes and to *avoid* disputes.

We believe the office can take a strong leadership role in fulfilling this function. We propose that the OCP take a more visionary approach and become active in tracking and facilitating combination product reviews. The OCP can serve to identify a point of contact in the consultative center and ensure that the project manager in the lead center has this contact information. The OCP can perform periodic checks during the submission review to track milestones such as delivery of submission materials to the consulting center, return of questions to be asked of the sponsor from the consulting to the lead center and resolution of issues that arise during the review. These activities would be helpful in truly coordinating and expediting the review of the combination product application.

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***Pharmaceutical Research and Manufacturers of America***

Specific Comments:

*The document could be improved with a better definition of "timeliness."*

According to the draft "a timeliness dispute arises when FDA does not review and act on an applicant's submission within the applicable time frame". It would be worthwhile to add clarifying text to the guidance document and to provide an example of a typical dispute timeline. Please note that timeliness is more than time to an action date. Timeliness encompasses execution of good review practices, appropriate supervisory review within FDA throughout the review process (not just at the conclusion), communication during the review process with the sponsor, and clear articulation of any questions that arise during the review.

*More specific information regarding the coordination of reviews and performance goals under PDUFA and MDUFMA would be greatly appreciated.*

We are concerned with differences existing between the Prescription Drug User Fee Act (PDUFA) performance goals and the Medical Device User Fee and Modernization Act (MDUFMA) performance goals going into effect in the year 2005. Depending upon the components of the combination product and type of premarket application submitted, both PDUFA and MDUFMA performance goals might apply. As stated in footnote 2, page 2 of the draft guidance, under PDUFA, the FDA is required to act on 90 % of priority NDA and BLA submissions within 6 months. Under MDUFMA, FDA is to issue 75% of its major deficiency letters on PMAs within 150 days, beginning in the year 2005. It appears that the MDUFMA review could possibly extend the overall review of the application until MDUFMA performance goals come into effect in 2005. It is unclear thereafter whether PDUFA and MDUFMA performance goals would be harmonized.

*In point 2 of Section III, we would like more information about how FDA will obtain agreement from the consulting center to perform its review within the lead center review time when the lead center has the shorter performance target.*

We are concerned about situations where the lead center has a shorter performance target than the consulting center. There are also situations in which the consulting center may not have user fees or performance targets. Examples include a grandfathered drug or a new chemical entity for which a stand-alone indication has not been, and is not being, pursued that is sent to the Center for Drug Evaluation and Research (CDER) for consultative review. If a device manufacturer were to create a combination product with a one of these types of drug products and a device component that requires 510(k) clearance, the CDER review should be completed in the 90-day review time. It is unclear from the guidance document how this situation would be handled.

*In point 4 of Section III, it is not clear what performance goal would be applied and how the OCP would obtain compliance with the goal.*

The user fee goals are a useful reference point but there are some submissions that appear to fall outside these stated goals. For example, the PDUFA goals cover efficacy and manufacturing submissions but when there are labeling changes that are not associated with clinical or manufacturing changes, there are no specific goals defined.

A suggestion for the process of setting the review target would be for the sponsor and the OCP to discuss and agree on the review timing for the submission around the time of the submission. At that time the product concept and the submission contents would be well understood and agreement could be reached with regard to the level of involvement of each of the reviewing centers. This could be documented and the review time target could be clearly identified instead of remaining vague as it currently is in the guidance document. Also, it would be helpful to industry if the OCP would provide a method of gauging how the review is progressing.

*The review process and timing could be more efficient with active OCP involvement.*

Alignment of Center performance goals, as noted above, would not only help to clarify timeline expectations across centers, but would also compliment agency efforts to have Centers collaborate during the combination product review process. An example where center "silos" can have a negative effect is when a new combination product consisting of an approved drug product in its existing container is placed in a new disposable delivery device: the drug submission prior approval timing would be applied (21CFR 314.70(b)). The minimum review time for this would be 4 months with the review more likely to stretch to 6 months or more, yet the device review time would be 3 months. If the drug center would rely on the device center for the technical review, they could serve as primarily a processing center for the documentation. Applying the drug approval timeframe could result in an inefficient and unnecessarily lengthy review that could possibly be avoided with OCP involvement in the review logistics.

Conclusion:

From the draft document, it is clear that the lead Center is meant to stay as the industry liaison and that the OCP will not routinely get involved in the review issues per se. It would be appropriate for the OCP to assume a more active role in managing or coordinating the review of combination product submissions.

Lastly, it will be important to note in the final guidance that the OCP will work directly with the Sponsor in some instances, and to provide examples of when that might happen.

Thank you for considering these comments as you finalize the guidance. Please contact me if you have any questions.

Sincerely,



Alice E. Till, Ph.D.

CC S. O'Shea  
S. Lard-Whiteford  
L. Weinstein  
W. Rumble