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Dockets Management Branch (HFA-305)  
**Food and Drug Administration**  
5630 Fishers Lane  
Rm. 1601  
Rockville, MD 20852

Re: **Docket No. 2004D-0182**

Eli Lilly and Company is pleased to have the opportunity to comment on the subject draft document. We fully support the establishment of the new Office of Combination Products and the activities that are underway to clarify the regulation of combination products.

Attached are Eli Lilly comments on the draft guidance document. General concerns are presented first, followed by comments about specific sections of the guidance.

Please feel free to contact me at (317) 433-9882 for clarification of any comments.

Sincerely,

Diane Zezza, PhD.  
Director, Global Regulatory Affairs,  
Chemistry Manufacturing and Control

2004D-0182

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Eli Lilly and Company

**Comments to FDA Draft Guidance for Industry  
Combination Products  
Timeliness of Premarket Reviews  
Dispute Resolution Guidance  
Docket No. 2004D-0182**

Eli Lilly and Company welcome the opportunity to provide comments on the proposed guidance document "Combination Products, Timeliness of Premarket Reviews, Dispute Resolution Guidance". We fully support the establishment of the new Office of Combination Products and the activities that are underway to clarify the regulation of combination products.

*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". This is further supported on the FDA website page that provides an overview of the OCP where one of the offices duties listed is "ensuring timely and effective premarket review of combination products by overseeing reviews involving more than one agency center". We see that there is an opportunity for the OCP to improve communication between reviewing centers so that disputes can be avoided.

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 steps would serve to coordinate and expedite the review of the combination product application and potentially avoid delays.

We believe that the OCP can promote 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.

*It would be helpful if the document contained more information about the coordination of reviews and performance goals under the PDUFA and MDUFMA legislation.*

We have noted that there are differences between the PDUFA performance goals and the MDUFMA performance goals that will go 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. In some situations the consulting center may not have user fees or performance targets, such as a generic drug reviewed by CDER. If a device manufacturer were to create a combination product with a generic drug 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. 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. In point 4 of this section, it is not at all clear what performance goal would be applied and how the OCP would obtain compliance with this goal.

A suggestion for the process of setting the review target would be for the sponsor and the OCP to discuss and agree to 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.

*The review process could be more efficient with active OCP involvement:*

Alignment of the various performance goals, as noted above, would help to clarify timeline expectations across centers and would compliment FDA 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 consists of an approved drug product in its existing container that 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 would serve as primarily a processing center for the documentation.

*Conclusion:*

From the draft document, it is clear that the lead Center will remain as the sponsor liaison and that the OCP will not get involved in the review process. It would be most helpful for the OCP to assume a more active role in managing the review of combination product submissions.