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

Re: **Docket No. 2004^N-0194**

Eli Lilly and Company is pleased to have the opportunity to comment on the proposed rule. 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 proposed rule. Two areas of concern about the proposed rule are presented.

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

Answers That Matter.

Eli Lilly and Company
Comments to FDA Proposed Rule
Definition of Primary Mode of Action of a Combination Product
Docket No. 2004N-0194

Eli Lilly and Company welcomes the opportunity to provide comments on the proposed rule “Definition of Primary Mode of Action of a Combination Product.” 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.

The proposed rule is most useful for those combination products that are physically, chemically or otherwise combined or mixed and produced as a single entity where the primary mode of action is not immediately evident. However, for combination products that are not produced as a single entity (e.g. separate products that are packaged together in a single package or unit and a product that is packaged separately but intended for use only with a specified regulated product), the proposed rule is not as helpful.

We have two areas of concern with the proposed rule:

Overly burdensome review

As we read the proposed rule, the primary therapeutic effect of all drug delivery devices would be that of the drug product. This would cause these products to have a more burdensome review requirement than is necessary. The situations we envision involve the creation of a combination product that combines a drug product in its approved container with no change to the route or method of administration. This container might be placed in a delivery device to create a disposable presentation or it might be used in a new reusable delivery device that identifies the drug product specifically.

Scenario 1: Under the proposed rule, the important therapeutic action of either of these combinations is defined to be that of the drug product. Therefore, a supplemental NDA would be required with CDER as lead reviewer. However, the bulk of the information contained in the submission would be related to the device component performance and instructions for use, areas in which CDRH has a greater level of expertise. The reviewing time is also a concern. The length of the review would be at least four months and possibly as long as six months because of the CDER performance targets while a device-only review could be three months. We believe that in this situation the review should be led by CDRH, since there are no new issues of safety and efficacy related to the drug product when used in combination with the new device portion.

Scenario 2: If the device platform were to be applied to different drug products in their approved containers, different CDER Divisions could be conducting reviews of the device information. This situation of multiple reviews could result in confusing or conflicting requirements for the release testing or labeling of the device. We believe

establishment of common requirements for a device platform would reduce the potential for inconsistencies among Divisions.

General delivery devices

Additionally, we are concerned that the proposed rule overlooks a category of products that we believe are combination products but are not identified in the combination product definition because a specific drug product is not identified in the device labeling.

In these devices the drug product is removed from the approved container and placed in another container such as a syringe or reservoir that consists of different material from the approved container. While this may not be an issue where the drug is intended to be in the new container for a short period of time, there are significant questions that can be raised when the drug is in contact with the new container for several hours or days. When the new material, different temperatures and other conditions are factored in, serious questions of drug stability and safety can be raised.

These devices may administer the drug via a route or method that is different from the approved indication (discrete injections versus continuous infusion). When these products are cleared without proper evaluation of the drug / device combination, new issues of safety and efficacy are not studied. The proposed rule does not address this gap.