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

RE: Docket No. 2005N-0098

Eli Lilly and Company is pleased to have the opportunity to comment on the topic of combination products and mutually conforming labeling. We fully support the efforts of the Office of Combination Products to clarify the regulation of combination products.

Comments of Eli Lilly regarding the hypothetical scenario described in the March 28, 2005 Federal Register Notice and discussed in the May 10, 2005 public meeting are attached. General concerns are presented and responses to the specific Public Health questions posed in the March 28 Federal Register Notices are provided.

Please feel free to contact me at (317) 276-4038 for clarification of any comments.

Sincerely,

Gregory G. Enas, Ph.D., RAC
Director, U.S. Regulatory Affairs
Eli Lilly and Company

Eli Lilly and Company
Comments to FDA Public Meeting on Combination Products and Mutually Conforming Labeling
Docket No. 2005N-0098

Eli Lilly and Company welcomes the opportunity to comment on the hypothetical situation posed by the FDA in the March 28, 2005 Federal Register Notice of Public Hearing and discussed in the May 10, 2005 Workshop, Combination Products and Mutually Conforming Labeling.

During the Workshop, it was suggested that the FDA should allow a device company to develop and market a combination product without the cooperation of the supplier of the drug portion of the combination. It was also suggested that the FDA could have the non-cooperative company modify their product labeling as a result of the introduction of the combination product. We disagree with this approach and urge the FDA to reject this as a possible option for combination products. In a similar vein, we also feel that it is inappropriate for proprietary information to be used during the review of a combination product without the agreement by the owner of the proprietary information.

When a device company develops a delivery method for a "category of drugs", we suggest that the CDER center responsible for reviewing that "drug category" be consulted to identify any issues related to drug stability and safety that should be addressed prior to clearance or approval of the device. We ask why it is important to evaluate compatibility of the drug and device only when the drug is specified on the device label, indeed couldn't similar questions be raised about compatibility of any drug (i.e. "drug category") that might be used with the device? With this in mind, we feel that it is important that the CDER reviewers be involved to ensure that all safety issues are identified regardless of whether the device is intended to deliver one drug or a category of drugs. If these issues are resolved satisfactorily through the device submission, we suggest that the companies that supply drugs in this category be allowed to add information about the delivery method in an annual reportable notification of changes to the label if they choose to do so. Reducing the regulatory burden in this way may encourage companies to proactively cooperate.

Finally, it would be very helpful for all involved with combination products and this issue of mutually conforming labeling if the FDA would provide clear definitions with examples of what is meant by "individually specified drug" (used in 21 CFR 3.2) and by "category of drugs" (used in the CDER / CDRH Intercenter Agreement). We also suggest that more information be provided regarding how CDER will be involved in developing these definitions.

We have prepared responses to the Public Health questions posed in the Federal Register Notice.

Public Health Issues

1. What are the product development implications of mutually conforming labeling? Are products not developed because of a perception that mutually conforming labeling will be, or might be, required?

Lilly comment:

We do not believe that a requirement of mutually conforming labeling would hinder the development of innovative products that can benefit the patients and satisfy unmet medical needs. On the contrary, we believe that it is important for the customer to have a complete picture of how to use an approved product for its intended indications including what delivery options are available for specific drug products or clear instructions on how to use a device and what drug products are appropriate to use with that device.

2. How important is it that drug and device labeling be consistent with respect to intended use, dose, dosage form, strength and route of administration for the safe and effective use of the drug and device together?

Lilly comment:

Given that in the example used by the FDA in the Federal Register Notice the drug is being used in a different indication, with a different set of supporting efficacy and safety data, there are in essence two distinct labels for the majority of sections of the label. If the FDA concludes that both labels should be associated with the drug or device, then they should be associated in their entirety with the exception of "How Supplied" section for the drug and the operator instruction for the device.

In the event that the indications are closely related (such as an insulin pump), the drug company would want to understand the technology and its safety and effectiveness. If the technology is truly safe and effective, the drug company would likely want to describe the device use in the label in order to avoid off-label uses.

It comes down to whether the device can be applied to a "category" of drugs and implications of complaints and liability to the drug application holder. Without cross labeling, the application holder would possibly view this as an off-label use and not proactively respond to adverse events and we feel that this is not an effective protection of public health.

3. Should the decision whether mutually conforming labeling is needed for the safe and effective use of the products together be made on a case-by-case basis? If so, what factors should FDA consider in determining whether mutually conforming labeling is necessary?

Lilly comment:

We believe that a general policy should be set with flexibility to allow possible deviations for unique or complex cases. In determining whether mutually conforming labeling is necessary, FDA should consider the impact that the non-conforming labeling could have on appropriate use of the combination product. They should also consider the risk that the inappropriate use represents to patient health.

4. To what degree should labeling conform? Does the labeling of the two products need to be identical? Consistent? Not contradictory? Is conformity more important for some parts of the labeling than others?

Lilly comment:

We believe that the labeling of the two products need not be identical in that all the drug information (cautions, warnings, etc.) need not be repeated in the device label or the device instructions for use need not be repeated in the drug label.

In the drug label, key device information needed to understand proper use of the combination, identification of the delivery options available or additional procedures that could be performed with the drug (e.g. electroporation) to enhance efficacy could be included. Proper guidance on the device operating parameters may be useful to guide the customer when choosing the type of device to use.

We strongly believe that the labeling of separately marketed drugs and devices should not be contradictory.

We recommend that the company that develops the labeling should propose the level of drug or device information that will provide the customer with what is needed to use the combination product effectively. We also suggest that the FDA consider the labeling proposed by the sponsor and labeling strategies followed for similar combination products when reviewing and negotiating the label contents in order to develop consistency in the labeling approach for combination products.

5. Under what circumstances can adequate instructions for use be conveyed in one product's label? For example, should FDA policy take into account the possibility that the labeling for a re-usable device might be lost over time?

Lilly comment:

If the drug and device are cross-labeled, it is not necessary to require complete instructions to accompany each component of the combination product. Should the re-usable device label be lost, it should be a simple matter for the customer to request a replacement instruction manual from the device manufacturer. Maintaining consistent information in both sets of labels between the two companies is impractical.

6. How should FDA policy take into account the possibility that the product for which no supplemental marketing application was submitted (i.e., the approved product) might be reformulated or redesigned? Is it possible for Company B to sufficiently monitor product A to ensure that Company B is aware of formulation changes? Is it possible to identify in advance the characteristics of product A that should be monitored?

Lilly comment:

In the case of drug product, it is not possible to monitor the drug product to detect reformulation scenarios unless the drug and device are cross-labeled. If the drug product is reformulated in a way that could cause a safety issue, the public will be at risk because a monitoring program is not practical to administer. Mutually conforming labeling is the most effective way to prompt the drug company to evaluate the implication of the reformulation on delivery methods.

It is not completely possible to identify in advance the characteristics of product A that should be monitored. However, it is possible to mitigate the risk of redesign of the device. Assuming that the critical parameters of the device performance have been identified and the device redesign does not affect the critical parameters and performance, this would not be an issue. The limitation is the extent of the understanding of the critical parameters of device performance as they relate to the delivery of the drug product.

7. If mutually conforming labeling is not always required, what process should FDA follow in order to determine when it is required and when it is not required? When is the best time in the review process to make this determination?

Lilly comment:

In all cases, general considerations of applicability of the biocompatibility testing performed on the device materials, the stability testing performed by the drug company,

and any changes to these two that may impact drug quality, potency, etc., must be considered. If parameters can be set, then these might guide when mutually conforming labeling is not necessary. Also changes in population, indications, dosing, mode of administration should require some alteration of the drug product label in order to safeguard public health.

The best time to determine the need for mutually conforming labeling should be early in the development process (i.e., in the Request For Designation stage) and not wait until the review of the application.