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From: ALLISON\_CHRISTINE@LILLY.COM  
Sent: Thursday, January 23, 2003 10:04 AM  
To: FDADockets@oc.fda.gov  
Cc: ALLISON\_CHRISTINE@LILLY.COM; MKramer@oc.fda.gov  
Subject: Lilly Comments to FDA Regulation of Combination Products (Doc  
ket No. 02N-0445)

Please see attached file for comments.

Regards,  
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*Lilly*

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January 23, 2003

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane., Rm. 1061  
Rockville, MD 20852

Re: [Docket No. 02N-0445] FDA Regulation of Combination Products; Public  
Hearing

Dear Madam or Sir:

Eli Lilly and Company are pleased to have the opportunity to provide comments on the questions posted in the Federal Register for the above Public Hearing held on November 25, 2002.

Attached please find our comments to each question posted for the Hearing.

Please feel free to contact me at (317) 433-9882 or Christine Allison at (317) 276-9383 for clarification of any comments.

Sincerely,



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

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Answers That Matter.

**Eli Lilly and Company**  
**Comments to FDA Regulation of Combination Products**  
**Docket No. 02N-0445**

*A. Assignment and Intercenter Agreements*

**Question 1: What types of guiding scientific and policy principles should FDA use in its revisions to the existing Intercenter Agreements that allocate review responsibility for human medical products?**

Lilly Comments:

A rewrite is necessary as the existing Intercenter Agreements are out of date, particularly considering the recent consolidation of parts of CBER within CDER. We suggest that the new Office of Combination Products not only designate the lead reviewing Center, but also identify what other consulting centers will be involved in the review of the application. Lilly sees administrative oversight as a key role to be played by the new office. This should allow timelines to be maintained through management of the overall review process and the isolation of sponsors from potential intercenter disputes over competing priorities and resource constraints. Beyond overview and dispute resolution of initial premarket review of combination products, Lilly suggests that this office stay involved in overview and dispute resolution of post-market regulation of these products.

**Question 2: What factors should FDA consider in determining the primary mode of action of a combination product? In instances where the primary mode of action of the combination product cannot be determined with certainty, what other factors should the agency consider in assigning primary jurisdiction? Is there a hierarchy among these additional factors that should be considered in order to ensure adequate review and regulation (e.g., which component presents greater safety questions)?**

Lilly Comments:

Lilly's current involvement with drug/device combination products centers mainly on reusable and disposable mechanical drug delivery systems (e.g., pen-injectors). Here, primary mode of action is relatively straightforward; the primary mode of action is a "drug." However, we believe that each drug/device scenario should drive the lead center decision as well as the appropriate submission type. We believe this is consistent with the FDA's definition of a combination product and the efficiencies anticipated for such reviews.

For example, if only the drug is unapproved, CDER should take the lead to evaluate safety and efficacy of the specified delivery method without revisiting device data previously reviewed by CDRH. Alternatively, once a drug formulation has been demonstrated to be safe for a specific route of delivery, the data should not be reevaluated when a new device is introduced.

Table 1 summarizes Lilly's recommendation for various drug/device combination product submission scenarios. Questions 4 and 7 provide additional perspective regarding these scenarios.

Table 1: Lilly Recommended Lead Center and Submission Type

<i>Drug/Device Combination Product Submission Scenarios</i>					
<i>Product Type</i>	<i>Drug Portion</i>	<i>Device Portion</i>	<i>Lead Center</i>	<i>Consulting Center</i>	<i>Submission</i>
Disposable*	New (drug)	New	CDER	CDRH	NDA
Disposable	Previously approved	New	CDER	CDRH	§314.70(b) for drug, 510(k) for device
Disposable	New (drug)	Previously approved	CDER	CDRH	NDA
Disposable	New (container closure)	Previously approved	CDER	CDRH	§314.70(b)
Disposable	Previously approved	Revision would require 510(k)	CDER	CDRH	§314.70(b) for drug, 510(k) for device
Disposable	Previously approved	Revision would not require 510(k)	CDER	CDRH	§314.70(d)
Reusable**	New	New	Dual	NA	NDA for drug, 510(k) for device
Reusable	Previously approved	New	Dual	NA	§314.70(d) for drug, 510(k) for device
Reusable	Previously approved	Revision would require 510(k)	CDRH	NA	510(k) for device
Reusable	Previously approved	Revision would not require 510(k)	NA	NA	None

\* Disposable product where drug and device are permanently integrated at point of manufacture

\*\* Reusable product where drug and device are manufactured separately

## *B. Marketing Applications*

**Question 3: What are the general scientific and policy principles that should be followed in selecting the premarket regulatory authorities to be applied to combination products? Is one premarket review mechanism (e.g., premarket approval [PMA], premarket notification [510(k)], new drug application [NDA], or biologic licensing application [BLA]) more suitable than another for regulating combination products?**

Lilly Comments:

Lilly supports the concept of a single premarket review mechanism leading to a single approval of the combination product. However, Lilly does not believe that one premarket review mechanism is more suitable than another for regulating combination products. When submitting a single application, we recommend applying the applicable regulations to the appropriate portion of the product for premarket review and approval. Device regulations should be applied to the device portion and drug regulations should be applied to the drug portion. The device information should always be formatted for device reviews [PMA or 510(k)] and the drug/biologic information should always be formatted for drug reviews (NDA or BLA). This allows each center to review their relevant sections in a familiar and convenient format.

**Question 4: Recognizing the need to ensure product safety and effectiveness, what criteria should FDA use to determine whether a single application or separate applications for the individual components would be most appropriate for regulation of a combination product? For example, FDA may determine that it is necessary to apply elements of different regulatory authorities to a combination product to ensure safety and efficacy (e.g., device postmarketing reporting for the combination product, with drug current good manufacturing practices (CGMPs) applicable to the drug component only). Should the need to apply a mixed regulatory approach influence whether one application or two are more appropriate?**

Lilly Comments:

A single application to the lead center is appropriate for products where the drug and device are unapproved and permanently integrated at the point of manufacture (e.g., disposable pen-injector). That same center should be designated for expedited reporting of adverse events and device malfunctions.

However, two applications may be more appropriate when the drug and device are new and provided separately but must be used together (e.g., reusable pen-injector). For example, this approach would be useful and possibly essential, when the device and drug are manufactured by different companies. With dual submissions, overall market authorization for the combination product can be contingent upon approval of both

submissions. The new office should monitor the progress of these dual, linked submissions to ensure timely, preferably simultaneous clearance of the device and the drug. Whether a dual submission or a single lead-center submission, adverse event and device malfunction expedited reporting should be directed to the Center(s) responsible for the review process.

There is no clear guidance on how to handle product changes to the device portion of a combination product that is submitted to CDER in an NDA. Most changes for a product covered by an NDA require approval prior to implementation, but this is not the case for many types of changes to a 510(k) device. If a change does not alter performance, safety or the indication for use for the product, this change can be made to a device without FDA approval or even notification. Lilly does not believe that these types of changes should be handled differently when the device is associated with a drug. We recommend the use of the CDRH guidance document decision tree for deciding when to submit a 510(k). Lilly recommends that, if a change is made to a device portion of a combination product and the change does not alter performance, safety or the indication for use for the product, the company should follow the requirements of 21 CFR PART 820, Quality System Regulation. The data generated to support the device modification will be retained in the Design History File and made available to an FDA investigator if requested. If there is an open NDA for this combination product, the nonreportable device change can be communicated to CDER in the NDA Annual Report [21 CFR §314.70(d)]. If the decision tree recommends that a submission be sent, an NDA supplement that follows the 510(k) format will be sent for CDER to review in consultation with CDRH.

In general, 21 CFR PART 314 should apply to postmarket changes made to the drug portion and the 510(k) decision tree should apply to the device portion. For adverse event or device malfunction expedited reporting, 21 CFR PART 314 should apply to the drug portion and 21 CFR PART 803 should apply to the device portion. Similarly, 21 CFR PART 312 and 21 CFR PART 812 should be applied to the investigational drug and device expedited reporting, respectively.

When the device portion is either new or modified and the drug portion remains unchanged, review times should be consistent with the device regulations. In NDA supplements that provide modifications to only the device component of a combination product, we suggest that a system be developed to allow these modifications to be reviewed as if they were for a "pure" device.

*C. Other Issues*

**Question 5: What scientific and policy principles should be followed in determining the appropriate manufacturing and quality system regulatory authorities (e.g., Current Good Manufacturing Practices versus Quality System Regulation) applicable to combination products?**

Lilly Comments:

When the manufacturing of drug and device are completely separate, the device QSRs and the drug GMPs can be applied as appropriate. Clear policy is needed with regard to expectations for pre-approval inspections of combination products. It is our recommendation that the device production process should conform to the device regulations and the drug production should conform to the drug regulations. We have been informed by the Agency that the two Centers involved will coordinate the inspections to avoid duplication and that the investigators are to use the appropriate compliance program for guidance. In our experience, when CDER investigators have expressed interest in looking at the device process, they have admitted lack of knowledge and time to perform a thorough device inspection. It is important that the various center investigators are trained to perform the combination product inspections using all applicable regulations.

**Question 6: What scientific and policy principles should be followed in determining the appropriate adverse event reporting requirements (e.g., the drugs and biologics adverse event reporting system, Medical Device Reporting) to be applied to a combination product?**

Lilly Comments:

As previously discussed, the device regulations should be applied to the device portion and the drug regulations should be applied to the drug portion. These requirements should apply independent of whether the product has been approved through CDER (NDA, sNDA) or through CDRH [PMA, 510(k)]. Adverse event and device malfunction expedited reports should be directed to the same Center(s) that led the review and cleared the product.

As an example, a reusable insulin pen-injector cleared by CDRH [510(k)] and a disposable insulin pen-injector approved by CDER (NDA) are fundamentally the same; they are both precision devices for the delivery of insulin. If serious hypoglycemia were to occur due to a malfunction of the device, two interpretations of expedited reporting requirements are possible depending on which Center approved or cleared the product:

1. For the CDER-approved combination product, one might conclude that, as a drug, hypoglycemia is an expected adverse event with insulin therapy, which is expected, therefore not reportable.
2. For the CDRH-approved combination product, one might conclude that, as a device, expectancy of the event is not relevant and, therefore, the malfunction is reportable.

The similar quandary might exist for a CDER-approved combination product where device malfunction (reportable malfunction or unanticipated adverse device effect) does not involve an adverse event.

We believe that the rules for device malfunctions should apply to all drug/device combination products, independent of the primary review center. Given this belief, we recommend that the Office of Combination Products provide clarification regarding drug and device expedited reporting requirements for combination products (investigational and marketed products) reviewed and approved through CDER. Clarification should address the following for CDER-approved combination products:

- 1) Expedited reporting of device malfunctions with serious adverse events,
- 2) Expedited reporting of device malfunctions without serious adverse events but with the potential should they recur,
- 3) Timing for expedited reports (investigational and marketed CDER devices),
- 4) Which Center(s) should receive the expedited report(s).

Question 7: What other comments do you have concerning other issues related to FDA regulation of combination products? (Examples may include cross labeling of products intended to be used together, though manufactured by different companies; and application of promotion and advertising policies to combination products.)

Lilly Comments:

Cross labeling of products intended to be used together

For devices intended to be used with drugs that are already on the market, the inter-center agreement indicates that CDRH has the lead for regulation of the device and that the device and drug labeling must be mutually conforming. There is no guidance on how to obtain mutually conforming labeling or what is considered to be mutually conforming. Finally, there is no clear guidance on what changes need to be made to the drug labeling in order to reach conforming labeling and the drug submission regulations do not include this scenario of creating mutually conforming labeling.

It would save time and be more consistent with other devices that may be used with approved drugs (e.g., infusion sets, syringes and needles, etc.) if a general statement

could be placed on the drug labeling. This general statement would instruct the user to review the device labeling to ensure that the drug and device are compatible. Lilly suggests allowing the drug labeling to make general reference to devices designed and approved for the drug. This will avoid unnecessary drug labeling reviews for cleared devices. As an example, the approved European drug labeling (Summary of Product Characteristics) for one of Lilly's drug products states "...cartridges are to be used with a CE marked pen as recommended in the information provided by the device manufacturer." If a general labeling statement is not acceptable, we suggest allowing the cleared device to be included in the drug labeling as appropriate and the communication of that labeling change be made in the Annual Report [21 CFR §314.70(d)].

In our experience, device submission reviews at CDRH are generally completed within the 90-day timing for a 510(k) review. In contrast, for a submission to add a cleared new device to the drug product label, we have experienced a situation where a CDER reviewer asked for prior approval [21 CFR §314.70(b)] supplements with device performance data included. This allows CDER to take 6 to 10 months review just to include a cleared device name on the drug label. Often this review time extends to a year or more.

Guidance also is required regarding the situation when two companies are not in alignment regarding compatibility issues. As an example, a new needle manufacturer labels their product for use with an approved pen/cartridge system when the pen/cartridge manufacturer(s) disagree with that assessment. We suggest that the Office of Combination Products could serve as a resource for mediating and helping the manufacturers and the participating FDA Centers resolve this conflict.

#### Additional issue

Lilly has experienced significant delays in adding names of cleared dose delivery devices to drug product labeling in situations where the drug product contacts the device material. We have found that these situations are not handled as drug/device combinations and the requirements for obtaining approval is not clear. We encourage the Office of Combination Products to evaluate these situations and work with CDER and CDRH to define the data requirements for these combinations to ensure timely approval of these new indications and realization of mutually conforming labeling.