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

Re: **Docket No. 2004D-0431**
**Draft Guidance for Industry and the Food and Drug Administration; Current Good Manufacturing Practices for Combination Products**

Eli Lilly and Company appreciates the opportunity to comment on the draft *Guidance for Industry and FDA: Current Good Manufacturing Practice for Combination Products.* We commend the FDA for its efforts in formulating regulatory policies as well as for developing guidance to clarify regulations related to combination products.

Attached are Eli Lilly comments on the draft guidance document. Please feel free to contact me at (317) 277-1880 for clarification of any comments.

Sincerely,

Frank M Deane

Frank M. Deane, PhD.
Vice President, Quality

**Lilly Comments to FDA Draft Guidance for Industry and FDA:**
**Current Good Manufacturing Practice for Combination Products**
**Docket No. 2004D-0431**

Eli Lilly and Company appreciates the opportunity to comment on the draft *Guidance for Industry and FDA: Current Good Manufacturing Practice for Combination Products*. We commend the FDA for its efforts in formulating regulatory policies as well as for developing guidance to clarify regulations related to combination products, especially those relating to the applicability of CGMPs to the manufacture of combination products.

We support the position described in the guidance that each constituent part remains subject only to its governing current good manufacturing practice regulations when marketed separately, and when manufactured separately as constituent parts of a combination that will later be combined. We also support the position that for combination products that are produced as a single-entity or are co-packaged, relevant portions of both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together.

We agree with the position that certain portions of one set of regulations should not necessarily apply to the components of a combination product after they have been combined. As the manufacturer of combination products, we believe we are best able to assess how to apply these aspects of the regulations to the combination product components during and after combining them in the final product to ensure compliance with both the CGMP and the QS regulations. We appreciate that FDA is encouraging manufacturers to seek FDA comment on their proposed implementation of CGMPs during pre-investigational meetings and throughout combination product development. We especially welcome the FDA's proposal to document its recommendations concerning the manufacturer's proposal and communicating this information to the appropriate District Office.

The following specific comments are provided for the Agency's consideration:

**Section I. (Lines 14-30)**

In this section of the draft Guidance, current good manufacturing practices are described as intended to ensure that "the product complies with performance standards as appropriate for the marketed combination product". We believe that the term "performance standards" should be used cautiously because it has a specific regulatory meaning in the context of medical devices. Many medical devices do not have established "performance standards". All are, however, expected to meet applicable requirements, which may include performance and/or voluntary standards and product specifications.

**Section III. A. (Lines 134-143)**

FDA highlights two specific examples, one involving "calculating the yield" and the other "corrective and preventive action." In each example, one set of regulations contains express/specific requirements while the other contains only general principles.

It would be appropriate to also include in this section a discussion of the quality planning and design control elements of QS regulations (21 CFR 820.20(d) and 820.30, respectively). While some aspects of these are touched upon in 21 CFR 211.22(a) and 210.3(b) (15), there are fundamental differences, most notably the concept of the Quality Plan as an overall roadmap to ensure compliance during all stages of development, which are worthy of emphasis.

**Section III. C. (Lines 240 - 241)**

We believe the statement "Combination products with constituent parts that are separately marketed but intended to be used together..." needs to be clarified with respect to the word "marketed". For example, one possible scenario is that the two constituents of the combination product may have to be stored at different temperatures and distributed separately. So the constituent parts are not "marketed" separately. They may be supplied in separate packages but they will be marketed together. We suggest the word "marketed" be changed to "packaged" as stated in 21 CFR 3.2(e)(3) and (4) for the definitions of combination products.

**Section IV. A. (Lines 254 – 272)**

We support the concept that sponsors and manufacturers meet with FDA early in the development phase to discuss a GMP plan. We suggest that the quality system plan that is ultimately agreed to be shared with investigators prior to facility inspections.

**Other clarifications**

The phrase "during and after joining together" is used throughout the document. It is possible to define this phrase in a variety of ways. It could mean as the component parts are received and accepted in the warehouse, or when they are placed on the manufacturing line, or when the components making up the combination product are physically joined. We recommend that the FDA allow the manufacturer to define how the two regulations will be applied to the constituent part throughout the manufacturing process and discuss this with the FDA during the discussions described in Section IV. A.

We support FDA's efforts to clarify the regulations and develop policies to address various issues regarding combination products. We look forward to continuing to work with FDA in this area.