



Alice E. Till, Ph.D.

VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS

December 3, 2004

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

Re: Draft Guidance for Industry and the Food and Drug Administration; Current Good Manufacturing Practices for Combination Products [Docket No. 2004D-0431, 69 *Federal Register*, 59239 (October 4, 2004)]

Dear Madam/Sir:

The following comments on the subject draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. Investing more than \$32 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA supports the concept described in the draft guidance that each constituent part remains subject only to its governing current good manufacturing practice regulations when marketed separately and when manufactured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 concept that relevant portions of both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together.

PhRMA welcomes the concept described in the guidance document specifically allowing that certain portions of one set of regulations do not necessarily apply to the components of a combination product after they have been combined. We welcome the concept that the sponsor can define how best to apply the aspects of these regulations to the combination product components during and after combining them in the final product. We are very encouraged that the Food and Drug Administration (FDA or Agency) is embracing the concept of establishing the GMP plan between the Agency and the sponsors early in the development stage and involving all reviewing centers/divisions and the manufacturers in the process.

The specific comments that we have regarding this document are as follows:

2004D-0431

C3

Pharmaceutical Research and Manufacturers of America

Section II. C. (Line 76-84)

The guidance describes how the primary mode of action determines the Agency component responsible for premarket review of the product. It further states "The lead center generally has responsibility for oversight of the regulation of the combination product, including the evaluation of current good manufacturing practice."

Using a drug/device combination as an example, we are concerned that the lead reviewing center may have the tendency to solely apply either the cGMPs or Quality System Regulations (QSRs) on both constituent parts of the combination product according to their expertise and experience instead of requesting assistance from the consulting center. We would like to see clarification in this paragraph that the cGMPs apply to the drug part and the QSRs apply to the device part and that qualified FDA experts review compliance of the constituent parts to the appropriate regulation or delegate the review to another Agency component that is specialized in that constituent.

We recognize that it is described later in the document regarding which regulations apply to the constituent parts (lines 148-151), but our point is that headquarters' CMC reviewers and the Compliance / ORA Field officers are usually specialized in either the drug cGMP regulations or the QSRs. If the primary mode of action (PMOA) group is responsible for the oversight of the combination product, including the evaluation of cGMPs, they need to either be cross-trained or prepared to delegate to one of the other groups so that the goal of "consistency and appropriateness" can be achieved.

Section III. C. (Lines 240 - 241)

The statements "Combination products with constituent parts that are separately marketed but intended to be used together..." may need 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 that the word "marketed" be changed to "packaged" as used in the combination product definition [21CFR 3.2 (e)(3) and (4)].

Section IV. A. (Lines 254 – 272)

We support the concept described in the guidance for sponsors and manufacturers to meet with FDA early in the development phase to discuss cGMP plans. In this meeting all parties involved should be invited. This means reviewers from lead and consulting centers, experts in the Offices of Compliance in the lead and consulting centers and the district office, and the Office of Combination Products. This will minimize confusion and promote "one FDA decision" from the Agency. We recommend that any discussions with Center and Field participants take place at the same time, by telephone if necessary.

We suggest that the quality system plan that is agreed to during the meeting with the FDA be used by FDA inspectors in the appropriate District Office as the blueprint during their investigation of the plant site. At this time, an investigator performs their inspections according to a specific regulation, either cGMP or QSR. This is not appropriate for a combination product where, as noted by the guidance document, certain aspects of the regulations do not apply. If a clear definition of how the two regulations are applied by the manufacturer is prepared and agreed to between the FDA and the manufacturer, it would be logical for the inspector to use this information. This should also apply to the inspections for manufacturing sites located overseas.

There are currently many activities underway addressing mutual recognition. Please clarify how the concepts of this document will be considered during the preparation of mutual recognition agreements.

In some situations, ICH guidance may govern data to be generated, for example, ICH guidance documents describe stability studies to be performed for drug products; however, there is nothing comparable for the device side. Please provide additional guidance on how this might be handled by the FDA.

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. A clearer definition of the FDA’s expectations would be helpful. Alternatively, we prefer that the manufacturer define how the two regulations will be applied for the components throughout the manufacturing process and discuss this with the FDA as described above.

We appreciate the opportunity to comment on this draft guidance and thank you in advance for your consideration of these comments as you finalize the guidance. Please contact me if you have any questions.

Sincerely,



Alice E. Till, Ph.D.

CC P. Love