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Friday, December 3, 2004

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

**Re: Docket No. 2004D-0431 – Comments on Draft Guidance for Industry and FDA Staff: Current Good Manufacturing Practices for Combination Products**

Dear Sir or Madam:

AdvaMed respectfully submits these comments to the Food and Drug Administration (FDA) in response to an October 4, 2004 notice requesting comments on the Agency's draft guidance document "Current Good Manufacturing Practice for Combination Products."

AdvaMed, the Advanced Medical Technology Association, represents more than 1,200 innovators and manufacturers of medical devices, diagnostic products and medical information systems. Its members produce nearly 90 percent of the \$75 billion in health technology products consumed yearly in the United States and nearly 50 percent of the \$175 billion purchased around the world annually. AdvaMed members range from the largest to the smallest medical technology innovators and companies. Nearly 70 percent of our members have fewer than \$30 million in sales annually. A significant and growing percentage of our member companies have health care products that incorporate combination technology, the subject of FDA's request for comments.

#### **GENERAL COMMENTS**

Thank you for the opportunity to comment on FDA's guidance document describing the applicability of current good manufacturing practices (CGMP) for combination products. We commend FDA's effort to bring clarity to the process. We believe that this document is generally a good first step toward the goal of providing clarity in that it provides an overarching framework. However, it lacks the specificity needed to ensure the application of consistent and appropriate good manufacturing practices. We look forward to

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working with FDA to further develop a guidance document that meets that goal and to commenting on these more specific recommendations as they are developed.

We strongly support the position taken by FDA 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 believe this approach is consistent with the spirit and intent of Section 503(g)(4)(D) of the Act.

## **SPECIFIC COMMENTS**

### **I. Co-Packaged Combination Products**

Section III. B. lines 159-161 of the guidance document states, "for combination products that are produced as single-entity or are co-packaged . . . both sets of current good manufacturing practice regulations are applicable during and after joining the constituent parts together."

We recommend differentiating co-packaged products from single-entity products, especially when the packaging process does not adversely affect the combination. It is not clear why packaging products together would in all cases change the constituent nature of the co-packaged product. One example of co-packaged products is device kits or trays (also known as convenience kits) that contain a finished drug. Consider how these provisions would apply to these products. What expectations warrant the application of the unique Quality System Regulations (QSRs), such as design controls, to the finished drug once joined with the device component of the combination product? What expectations warrant the application of the unique drug CGMP regulations, such as calculation of yield or stability testing, to the device component of the co-packaged combination? Generally, separately manufactured components packaged together do not change the constituent nature of the co-packaged product. We would be glad to work with the Agency to identify those situations where co-packaging should or need not require the application of both sets of regulations.

We recommend the Agency review the CDRH-CDER Intercenter Agreement which addresses the issue of convenience kits. Section VII, B.2 of the Intercenter Agreement provides that for convenience kits, in which CDRH is the lead Center, the device CGMPs apply. The agreement further states that changes to the drug during the processing require submission of an ANDA or NDA to CDRH. The Intercenter Agreement provides a clearer delineation of the applicable regulatory requirements to the co-packaged product. We believe that additional guidance regarding the application of CGMPs to co-packaged combination products should reflect this Intercenter Agreement.

Finally, we note that in addition to convenience kits, there are other co-packaged products that we believe also warrant segregable application of CGMPs or QSRs. Examples include disposable delivery systems co-packaged with drugs or biologics. This example highlights

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the need for FDA to provide greater clarification concerning those circumstances where co-packaged products should be treated like single-entity products for CGMP or QSR purposes.

## **II. Single-Entity Combination Products**

Section III. B. lines 171-174 states, "FDA believes that compliance with both sets of regulations during and after joining these types of combination products can generally be achieved by using either the CGMP or QS regulations, e.g., by using the current good manufacturing practice system already operating at a manufacturing facility."

We recommend that FDA further clarify that compliance with CGMP may be achieved by using one set of regulations, CGMP or QSRs, and by addressing relevant specific requirements specified by the other set of regulations. We also recommend that the center responsible for the essential set of regulations take the lead and coordinate inspections and compliance, with consultation as appropriate.

Table 1 appears to support the use of one essential set of regulations, supplemented as appropriate. If this is so, we support this approach and recommend that the guidance specifically state that "the manufacturer should comply with the set of regulations their quality system is based on and take into consideration the other current good manufacturing practice provisions which are listed in Table 1." We believe that Table 1 should be further clarified by supplemental guidance to "map" each section of the regulations to correlate specific elements of the regulation to the other regulation. We would be glad to work with FDA to develop this mapping analysis.

## **III. Combination Products Subject to 510(k) Submission**

Section IV. A. lines 254-262.

In the first paragraph under Section IV.A., FDA encourages manufacturers to discuss "with the Agency how current good manufacturing practice regulations apply to their products." While we support this approach, the paragraph also appears to assume that all single-entity products will be the subject of a premarket approval process (e.g., PMA or NDA). Given that the Intercenter Agreements were issued in the early 1990s and the likelihood that a number of drug-containing devices have come to market via the 510(k) process, the guidance should indicate a contact unit in CDRH where these matters can be discussed for a device that can come to market via the 510(k) process.

## **IV. Communication of Combination Product CGMP Compliance Plans/Information**

Section IV. A. lines 271-272 of the guidance document states, "Also, FDA staff should communicate this information to the appropriate District Office."

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To avoid confusion within the Agency, we recommend the FDA commit to sharing combination products CGMP compliance plans with the appropriate District Office. Specifically, we recommend modifying the last sentence of section IV. A., by replacing "should" with "will," so it reads "FDA staff will communicate this information to the appropriate District Office."

Because of the complexity associated with merging CGMP systems from the different center, we recommend FDA institute a proactive training program for field investigators to ensure appropriate and consistent treatment for combination products. Field training could also be supplemented by development of a Compliance Policy Guide specifically for Combination Products. The Agency may look to the excellent precedents of CDRH action when device GMP inspections were transitioned to the Quality System Inspection Technique.

#### **V. Guidance Document Reflect Quality Systems**

To reflect FDA's move towards Quality Systems, we recommend FDA consider changing the title of the document to "Guidance for Industry and FDA - Application of Quality Systems to Combination Products." In the final FDA quality regulations for devices (61 FR 52602), FDA changed the title of the regulation (part 820) from Current Good Manufacturing Practice (CGMP) to Quality System. In the draft guidance issued in September 2004 by FDA on Pharmaceutical CGMPs, the introduction indicates that the guidance will help manufacturers implement modern quality systems and risk management approaches to meeting CGMP regulations. It further states, "The guidance describes a comprehensive quality systems (QS) model...." Changing the title to QS more accurately reflects the systems approach that FDA has adopted for devices and is in the process of adopting for biologics and pharmaceuticals.

#### **CONCLUSION**

We appreciate the opportunity to share our concerns with and look forward to working with the Agency to address issues related to its combination products program. We especially believe that more discussion needs to take place around the issue of co-packaged and single-entity products. We respectfully request that such discussions take place before more specific guidance is developed in this area.

Respectfully submitted,



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**Total number of pages transmitted (including this page): 5 (five)**

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