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November 23, 2004

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

Ref.: "Draft Guidance for Industry and FDA: Current Good Manufacturing Practices for Combination Products," September 2004 submitted to Docket No. 2004D-0440, OC 2004219

Dear Sir/Madam:

PDA is pleased to provide comments on the FDA *Draft Guidance for Industry on Current Good Manufacturing Practices for Combination Products*, issued in September 2004. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological and device manufacturing and quality. A committee of interested industry representatives prepared the comments that follow.

PDA commends FDA's initiative to develop guidance for the application of quality system principles in the development and manufacture of combination products. We recognize that the diversity of combination product types make it necessary to begin by addressing fundamental principles in broad terms. We encourage FDA to develop additional and more detailed guidance on quality topics which, due to their complexity, are not addressed at this point in the evolution of thinking about quality systems for combination products. Since the initial guidance is of a general nature our comments have been kept to a high level. We have also included some suggestions indicating where more specific guidance is needed. PDA stands ready to participate in a process that will provide more detailed guidance in the future.

The following comments are provided for the Agency's consideration.

**Point #1**

**Introduction (lines 14-30)**

In the Introduction and elsewhere in the draft guidance, current Good Manufacturing Practices are described as intended to ensure that "the product complies with performance standards as appropriate for the marketed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." It is PDA's opinion that the term "performance standards," should be used cautiously since it has a specific regulatory meaning in the context of medical devices. Many medical devices do not have established "performance standards." They are, however, expected to meet applicable requirements, which may include performance and/or voluntary standards and product specifications.

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## **Point #2**

### **Current Good Manufacturing Practices: Background (lines 124-125)**

FDA states in the guidance that it considers the cGMPs and the Quality System regulations to be similar, and they are meant to achieve the same goals. There are differences in their implementation, including inspectional approach, and in requirement for pre-approval inspections (PAI) as a criterion for approval or non-approval. We encourage FDA to distinguish these differences and to provide further guidance with respect to their implementation.

## **Point #3**

### **Current Good Manufacturing Practices: Background (lines 134-143)**

FDA has highlighted two specific examples in which the express/specific requirements of cGMPs or Quality System regulations are not explicitly addressed in a corresponding regulation, but are addressed in a general sense. PDA recommends that FDA provide further detailed guidance for the examples provided. For example: with respect to the requirements for ensuring stability of a drug product (21 CFR 211.166) described in the first example, this is interpreted to be an ongoing requirement in support of commercialization of the drug product, whereas the design validation provisions (21 CFR 820.30(g)) imply a one time occurrence ("design validation shall be performed under defined operating conditions on initial production units, lots, batches, or their equivalent") unless the design changes.

It would be appropriate to also include in this section--perhaps as a third bullet point--a discussion of the quality planning and design control elements of Quality System regulations (21 CFR 820.3(d) and 820.30, respectively). While some aspects of these are addressed to a degree 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.

## **Point # 4**

### **Current Good Manufacturing Practices for Combination Products (Lines 160-161, 171-172)**

Throughout the document the phrase "during and after joining together" is used to describe the point at which industry must start to consider 21 CFR 210 and 211, and 21 CFR 820. It is unclear at what point in the manufacturing flow "during" occurs. For example: At constituent receipt? At the point of staging constituents on the manufacturing floor? When loading of constituents into a hopper? Or setting up on a packaging line? Clarification is needed to better interpret the FDA position with respect to "during and after joining together."

## **Point # 5**

### **Current Good Manufacturing Practices for Combination Products (Lines 180-184)**

There are several examples of components that are currently regulated via multiple regulatory pathways, and thus could potentially be subject to different governing current Good Manufacturing Practices regulations when marketed separately or as an integral part of a combination product.

An empty syringe, for instance, may be classified as a medical device, subject to pre-market notification requirements and the Quality System regulations. However, the same syringe is considered to be the primary container closure system of a drug or biologic system when marketed pre-filled with a drug or biologic. As such, it would be considered a packaging component, described in a Type III Drug Master File (DMF) and subject to cGMPs.

A combination product may also be manufactured using components that are not finished drugs, biologics or devices *per se*. Active pharmaceutical ingredients (APIs) or finished drugs may be combined with chemical, biological or device components (e.g., electrodes) producing a combination product regulated by CDER, and it is unclear as to which quality regulations might apply to these device-like elements.

PDA recommends that FDA provide guidance on how the cGMPs or Quality System regulations should be applied in such cases.

**Point # 6**

**Current Good Manufacturing Practice for Combination Products (Lines 205-217)**

FDA has suggested that manufacturers discuss their plans for achieving compliance with cGMPs and Quality System regulations with the Agency during the development of a combination product, either through meetings or during inspections. We recommend that FDA provide transparency of such agreements regarding application of current Good Manufacturing Practices regulations, as appropriate, to industry via the Office of Combination Products. PDA further encourages FDA to provide formal guidance in this area, rather than regulate on a case-by-case basis.

**Point # 7**

**Considerations for Different Types of Combination Products (Lines 221-247)**

It would be valuable for future guidance developed in this area to contain a discussion of the individual application of cGMPs and Quality System regulations as well as how to apply hybrid approaches to compliance throughout product lifecycle (i.e., from early development through manufacture and post-approval change) for the various categories of combination products.

We recommend that as the Quality System for pharmaceutical products concepts becomes more fully developed, more detailed guidance with respect to hybrid systems, which pose the greatest challenge to both industry and regulators, be considered as a priority.

PDA would be pleased to offer its expertise to assist in the clarification of its comments, and the continued evolution of this important guidance. We look forward to working with FDA, industry and other professional associations to develop a world class document.

Yours sincerely,



Victoria Ann Dedrick  
Vice President, Quality and Regulatory Affairs  
PDA