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February 4, 2010

Division of Docket Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

#### **Reference: 21 CFR Part 4, Current Good Manufacturing Practice Requirements for Combination Products, Docket No. FDA-2008-D-0409**

Dear Sir/Madam,

PDA is pleased to offer comments on the proposed rule under 21 CFR Part 4 titled "Current Good Manufacturing Practice Requirements for Combination Products". 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. Our comments were prepared by a committee of experts with experience in combination product issues, including members representing our Combination Products Interest Group and our Regulatory Affairs and Quality Committee. PDA appreciates the opportunity to offer comments on this proposed rule and wishes to thank FDA for the opportunity to do so.

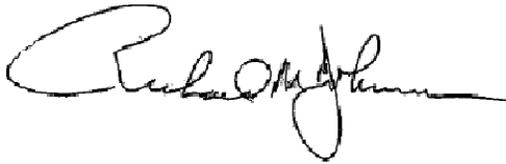
With regard to the proposed rule 21 CFR 4, "Current Good Manufacturing Practice Requirements for Combination Products", we have provided detailed comments identified by section of the proposed regulation and have included a supporting rationale in the accompanying table. In addition to the comments provided in the attached document, PDA would like to highlight two issues that we believe are broader than the specific comments enclosed. First, we would promote the use of the term Hybrid in place of Streamline throughout the document as we believe this reflects the true nature of the combining of two sets of regulations for combination products. Second, we would ask for clarification regarding existing products developed and approved prior to the finalization of CFR 4. The impact of this new regulation will be much greater on those existing products that have been developed and controlled with existing regulations and agreements and have been proven to be safe and effective.

In addition, we are concerned the proposed effective date of 180 days following publication of the final rule will not provide sufficient time for a thorough gap analysis, systematic design and implementation of changes necessitated by the combined sets of regulations for biologics, devices and drugs, and accordingly we suggest a 12 month post publication period for the regulations to become effective.

Again, PDA appreciates the opportunity to comment on this proposed rule and provides these recommendations for your consideration. PDA believes that these comments will clarify and strengthen the final rule to better serve the needs of both regulators and industry.

We would be pleased to offer our expertise in a public discussion and/or meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,

A handwritten signature in black ink, appearing to read "Richard Johnson". The signature is fluid and cursive, with a large initial "R" and a long horizontal stroke at the end.

Richard Johnson  
President, PDA

CC: Robert Dana, PDA  
Rich Levy, PhD, PDA

**PDA Comments; FDA Proposed Rule: Current Good Manufacturing Practice Requirements for Combination Products**

**February 4, 2010**

Level: 1 (High/Significant); 2 (Medium); 3 (Low – mainly editorial)

<b>Section</b>	<b>Proposed Change</b>	<b>Rationale</b>	<b>Level</b>
General	We propose the scope for the proposed rule should include the following statement: <u>“Convenience kits that contain device(s) and drugs or biologics would be governed under 21 CFR 4 ONLY if the device(s) included in the kit are Class II or III”</u>	Application of this revised approach to GMPs to all combination devices represents an unnecessarily burdensome approach to the industry and in most instances will not provide greater protection of the public health. We suggest a risk based approach that would apply 21 CFR 4 to only those combination products, including convenience kits, which include a Class II or III device.	2
	Recommend changing the wording throughout the proposed rule from "streamlined system" to "hybrid system".	In FDA’s Introductory section the term “streamlined cGMP operating system” is introduced and utilized to explain FDA’s approach to these proposed rules..  PDA agrees with the rationale made by FDA, but recommends that the term ‘hybrid’ replace “streamlined”. This replacement is suggested as the approach proposed by FDA is an appropriate melding (or hybridization) of current regulations, rather than a reduction in regulatory expectations which the term “streamline” implies.	1
<b>4.2</b>	Add: § 4.2: <i>Hybrid approach for combination product current good manufacturing practice operating systems</i> : means the incorporation of specific requirements from the drug cGMPs into the framework of a QS operating system for the drug constituent part, and vice versa.	To assure this approach is termed appropriately by Regulators and Manufacturers alike; PDA further recommends that this term be formally defined in §4.2 and appropriately utilized in §4.4	1

Section	Proposed Change	Rationale	Level
<p><b>4.4(b)</b></p>	<p>Revise 4.4(b)(1) If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the drug cGMPs, <u>the hybrid approach for combination product current good manufacturing practice operating systems may be applied and</u> the following provisions of the QS regulation must also be shown to have been satisfied <u>for the device constituent part</u>. Upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the QS regulation need be made.</p> <p>Revise 4.4(b)(2) If the combination product includes a device constituent part and a drug constituent part, and the current good manufacturing practice operating system has been shown to comply with the QS regulation, the hybrid approach for combination product current good manufacturing practice operating systems may be applied and the following provisions of the drug cGMPs must also be shown to have been satisfied for the device constituent part. Upon demonstration that these requirements have been satisfied, no additional showing of compliance with respect to the drug cGMPs need be made.</p>	<p>As currently written Section 4.4 may lead to the misinterpretation that the FDA is requiring single-entity and co-packaged combination products, as well as their constituent parts, to meet the identified requirements of both the drug GMP's and the medical device QSR's over the combination product's entire life-cycle. This misinterpretation would create a quality system requirement that exceeds historic and current FDA expectations. As a result of misinterpreting FDA's expectations, a misapplication of this Section may occur, resulting in a more demanding and complex quality system than that currently expected for non-combination medical products.</p> <p>This misinterpretation may lead manufacturers of currently approved combination products to impose new requirements and create unnecessary revision and complexity to their established quality control and assurance systems.</p> <p>Similarly misinterpretation of these requirements by developers of new combination products may cause them to forego product development or co-packaging presentations.</p>	<p>1</p>
<p><b>4.4(c) and 4.4(d)</b></p>	<p>Add the following to 4.4(c) - <u>. Device component and constituent parts are governed under QSR. The drug components and constituent parts are governed under cGMPs. The components of constituent parts would be governed under the quality system in which they are specified.</u>" and the following to 4.4(d) - <u>Hybrid approach for combination product current good manufacturing practice operating systems means the incorporation of specific requirements from the drug cGMPs into the framework of a QSR operating system for the drug constituent part, and vice versa.</u></p>	<p>The proposed regulation's use of the term "constituent part" may be misinterpreted to include drug and/or device component parts. PDA recommends that § 4.4 (c) and 4.4.(d) be rephrased to reduce the possibility of such misinterpretation.</p>	<p>1</p>

Section	Proposed Change	Rationale	Level
<b>Supplementary Information</b>	Add section II. E. <u>The enforcement of the proposed rule only be applied for new products being developed or those being modified to a future generation or design, and not applied retroactively to products approved and marketed prior to the issuance of the rule.</u>	The current document does not specifically discuss a "grandfather" clause so unclear what FDA's expectations are for products that were approved and marketed prior to implementation of these regulations.	1