CPC COMBINATION PRODUCT COALITION

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Mr. Mark D. Kramer
Director, Office of Combination Products
U.S. Food and Drug Administration
15800 Crabbs Branch Pkwy.
Suite 200 (HFG-3)
Rockville, MD 20855

Re: Increasing Transparency in the Application cGMP Regulations to Combination Products

Dear Mr. Kramer:

Thank you very much for meeting with the Combination Products Coalition ("CPC") on May 4, 2006, with regard to the status of various initiatives at the Office of Combination Products ("OCP"). We found the meeting to be tremendously helpful and productive, and we appreciate you and the other OCP representatives taking time to meet with us.

During the meeting, certain representatives of the OCP mentioned that they would be interested in the CPC's suggestions for bringing greater transparency to the application of current Good Manufacturing Practices ("cGMP")[1] regulations, and for ensuring consistency in enforcement issues, as these regulations are applied to combination products.

By way of background, the CPC is comprised of leading pharmaceutical, biological, and medical device manufacturers that have considerable experience with combination products, as well as their constituent product areas. We think that our

[1] For purposes of this letter, the term *current good manufacturing practice* refers to the current good manufacturing practice regulations for drugs and most biological products under 21 CFR Parts 210 and 211, for certain biological products under 21 CFR Parts 600-680, and the quality system regulations for devices under 21 CFR Part 820.

diverse membership allows us to bring a uniquely broad perspective to the issues facing the regulation of combination products, such as the application of cGMP regulations. With that background in mind, we offer the following thoughts and suggestions with regard to these issues.

I. General Suggestions

Without a doubt, one of the biggest concerns of an FDA-regulated manufacturer is regulatory compliance. Manufacturers want to comply with FDA regulations that apply to them for a variety of reasons, not the least of which is that a high level of compliance helps to ensure a high quality product that health professionals and patients can use safely and reliably.

In order to achieve a high level of compliance, though, manufacturers must first thoroughly understand how the regulations apply to them. Understandably, when cutting-edge technologies are concerned, the application of existing regulations and standards can be unclear or even downright confusing. Also understandably, crafting new policies and regulations can be a painstaking process that takes a tremendous amount of time and effort on behalf of both industry and FDA. Both applying the existing cGMP regulations to combination products, as well as drafting new rules for such products, are no exceptions. We understand that currently FDA predicts that a proposed rule on combination product cGMP is expected in the spring of 2007, and we would guess that a final rule is some years away.

While FDA is developing new regulations, though, manufacturers still need to comply with existing regulations. Therefore, the CPC believes that the agency should implement tools to facilitate understanding of the application of existing cGMP regulations to combination products. We describe our specific suggestions in detail below.

II. Specific Suggestions

A. Web-Based Information

Through its website, the OCP shares a wealth of information with regard to the request for designation ("RFD") process and jurisdictional decisions.[2] Frankly, we have found this information to be extremely helpful in determining which FDA Center is the "lead" for a particular product and for developing RFDs. In a similar vein, we believe that analogous information with respect to the application of cGMP regulations to combination products would be tremendously useful in helping industry achieve compliance with the appropriate cGMP regulations. More specifically, the CPC suggests that the OCP post on its website the following information with regard to the application of cGMP regulations:

[2] See FDA, OCP, Jurisdictional Updates, *available at*: http://www.fda.gov/oc/combination/updates.html.

- GMP Updates – This would consist of in-depth summaries of past decisions addressing how cGMP regulations apply to combination products.
- Agency Decisions – The agency should post redacted agency decisions concerning the applicability of cGMP regulations to combination products. "Agency decisions" are what a firm receives from FDA regarding cGMP issues as applied to combination products, for example, warning letters, informal correspondence such as meeting minutes, and advisory opinions.[3]
- GMP Determinations – This would consist of one-line summaries of decisions the agency has made with regard to the applicability of cGMP regulations to individual combination products.
- Pertinent guidance documents and other FDA documents, for example, manual updates.

We also believe that this information has the advantage of being readily accessible to FDA for sharing. While in some cases FDA would need to draft summaries and redact information, we expect that this work could be accomplished relatively quickly. The CPC is also happy to assist the agency in any way that it can in order to expedite the sharing of this information.

With regard to implementing this suggestion, we have heard that the agency is concerned that Good Guidance Practices ("GGPs") apply to sharing this information on its website. We would like to take this opportunity to address that concern.

GGPs include the agency's policies and procedures for developing, issuing, and using guidance documents. Among other things, GGPs provide for public input and participation in the development of "guidance documents." The GGP regulation defines a "guidance document" as "documents prepared for FDA staff, applicants/sponsors, and the public that describe the agency's interpretation of or policy on a regulatory issue."[4] The GGP regulation also provides that guidance documents do not include:

> Documents relating to internal FDA procedures, agency reports, general information documents provided to consumers or health professionals, speeches, journal articles and editorials, media interviews, press materials, warning letters, memoranda of understanding, or <u>other communications directed to individual persons or firms</u>.[5]

GGPs must be followed "whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience."[6]

[3] See II.B., regarding Advisory Opinions.
[4] 21 C.F.R. § 10.115(b)(1).
[5] § 10.115(b)(3) (emphasis added).
[6] § 10.115(e).

The information that we are suggesting OCP share includes things like summaries of past decisions, warning letters, and meeting minutes. These communications were directed to individual combination product manufacturers and address the application of cGMP regulations to particular combination products. They fit squarely within communications to which GGPs do not apply -- "communications directed to individual persons or firms."[7] Because of this, GGPs do not apply to what we are suggesting FDA share on its website.

We acknowledge that we are suggesting that these one-on-one communications be shared with a broad audience; however, merely sharing that information does not mean that the communications are a "guidance document" that is governed by GGP. All over its website, FDA posts a variety of manufacturer-specific communications that are helpful to industry. For example, in addition to the jurisdiction-related information that we've already mentioned, FDA also posts selected EIRs and 483s, untitled letters, and warning letters. Manufacturers use this information to guide their own compliance decisions, to the benefit of FDA, industry, and ultimately, patients. GGPs are tremendously important, but they do not impede FDA sharing product-specific interpretations with industry.

We do want to mention, though, that on the OCP webpage where the jurisdiction-related information can be obtained, the agency provides: "It should be noted that jurisdictional updates report prior Agency decisions only and are not policy statements." Though probably not required, we think that a "disclaimer" such as this would be appropriate for the similar cGMP information.

B. Field Force Consistency

During the May 4 meeting, the CPC and OCP discussed the variations among FDA's field offices with regard to enforcement of cGMP regulations as applied to combination products. We've given this issue considerable thought and offer two key suggestions for addressing and improving the consistency and knowledge base of FDA's field force with respect to the application of cGMP regulations to combination products.

1. Field Force Training and Coordination

First, because of the complexity of the different cGMP regulations and systems for drugs, biologics, and devices, inspecting combination product manufacturers for compliance with the cGMP regulations requires appropriately trained and experienced inspectors. To ensure that this occurs, the field force should first be alerted that an inspected firm manufactures combination products. We believe that a process should be developed to ensure that the field is alerted when an inspected product is a combination product, to the extent that such a process does not already exist.[8]

[7] § 10.115(b)(3).

[8] We understand that currently, the field force may be sent some portion of an NDA or other documentation for combination products where CDER is the lead Center, but that the field force may not

The CPC also believes that inspectors charged with responsibility for inspecting combination product manufacturers should be cross-trained on applicable regulations. The CPC further believes that in certain instances, inspection by a team of two or more inspectors with complementary knowledge, skills, and experiences may be appropriate.

However, while these suggestions are easy to state, their implementation issues can be decidedly more complex. Therefore, to facilitate their implementation, the CPC suggests that FDA develop procedures relating to the inspection and enforcement of cGMP regulations as applied to combination products. Below are the key issues the CPC believes FDA should address in these procedures:

- How the agency ensures that an inspector who inspects a combination product manufacturer has been appropriately trained.
- Criteria for determining whether a manufacturer's cGMP system can be adequately inspected by a single inspector who has been cross-trained or whether separate inspections of cGMP components are needed.
- How assignment of the lead center for regulating a combination product affects assignment of inspection personnel (e.g., Will "lead" inspection personnel vary depending on the assignment of a lead center?)
- How the agency ensures consistent treatment of similar combination products.

The CPC believes that FDA must give careful thought and consideration to these and related issues to ensure that cGMP regulations are appropriately applied throughout the combination product industry. In other areas of inspection and enforcement, FDA has internal procedures that agency staff follows to ensure efficient, fair, and thorough inspections of manufacturers.[9] The combination product industry should be no different.

In addition to these questions, we would also encourage FDA's input on what role manufacturers can usefully play in developing appropriate solutions and in exchanging ideas related to training and development of personnel. Speaking for ourselves, the CPC would be happy to assist the OCP in formulating answers to these and other related questions that arise with respect to inspection and enforcement of cGMP regulations.

2. Process for Addressing Inconsistency Issues

Second, we believe that FDA should define a clear process for manufacturers to raise suspected instances of inconsistency in the application of cGMP regulations to combination products by the FDA field force. In particular, OCP should specify who at the agency will address inconsistency issues and should ensure that all relevant agency

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receive analogous information for combination products where CDRH is the lead Center (e.g., copies of the PMA).

[9] *See e.g.*, FDA, Office of Regulatory Affairs, Investigations Operations Manual (2006), Sections 5.4 (Food), 5.5 (Drugs), 5.6 (Devices), and 5.7 (Biologics); *see also* FDA, Office of Regulatory Affairs, Compliance Program Guidance Manual.

components are involved and informed of the outcome. In addition to enabling the agency and industry to identify and address inconsistency issues on a case-by-case basis, such a process would also enable FDA to identify areas of education and training for field office personnel and areas where industry needs more guidance on the application of cGMP regulations to combination products.

The CPC further suggests that the OCP consult with FDA's Office of the Ombudsman when developing this process, as the Ombudsman's Office is uniquely skilled in addressing issues of this type. Indeed, the Office's website describes its main function as being "to explore complaints and assist in resolving disputes between companies or individuals and agency offices" and further provides that the Office often addresses "claims of unfair or unequal treatment."[10]

C. Additional Guidance

As FDA is aware, combination product manufacturers have numerous questions about the application of cGMP regulations to combination products. Currently the agency is developing a proposed rule for cGMPs that apply to combination products, and the CPC wholeheartedly supports that effort. In the interim, though, combination product manufacturers must continue to rely on statements of FDA's current thinking on the application of cGMP regulations to combination products. This current thinking is represented by things such as agency statements, interpretation of existing regulations, and the "Draft Guidance for Industry and FDA: Current Good Manufacturing Practices for Combination Products". Although this is helpful, the CPC strongly believes that the agency should provide additional guidance on the application of the cGMP regulations. Without further guidance, waiting years for regulations to be promulgated puts an enormous strain on industry.

The members of the CPC have found that a "Frequently Asked Questions" format is extremely helpful in other areas of FDA regulation and believes that a "cGMP Regulation FAQ" would serve industry and FDA well. The CPC is currently drafting a FAQ document and will submit it to the agency soon as proposed guidance.

As a part of that guidance, the CPC also believes that the agency needs to provide more specific guidance on how cGMP regulations will be applied to particular types of combination products. More specifically, we see a critical need for guidance that uses specific case studies and examples to illustrate the agency's thinking. FDA has a tremendous opportunity to use its scientific expertise and experience to develop thoughtful and practical guidelines that will ensure consistent and predictable application of the regulations, and we urge the agency to maximize this potential. We will propose some case studies as part of the FAQ document we are developing.

III. Conclusion

[10] FDA, Office of the Ombudsman, http://www.fda.gov/oc/ombudsman/homepage.htm and http://www.fda.gov/oc/ombudsman/whencon.htm.

The CPC appreciates the agency taking time to meet with us on May 4 and also appreciates the opportunity to provide these suggestions for improving the transparency of the application of CGMP regulations to combination products. As always, we are happy to assist in any way that we can.

Respectfully submitted,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition