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November 14, 2011

Division of Dockets Management (HFA-305)  
U.S. Food & Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Docket No. FDA-2011-D-0567; Draft Guidance for Industry, Clinical Investigators, and Food and Drug Administration Staff; Design Considerations for Pivotal Clinical Investigations for Medical Devices

Dear Sir or Madam:

The Combination Products Coalition (“CPC”) commends the U.S. Food and Drug Administration (“Agency”), and in particular the Office of Combination Products (“OCP”), on its attention to issues affecting combination products and how best to serve patient needs with respect to such products. In this letter, we offer our comments on the *Draft Guidance for Industry, Clinical Investigators, and Food and Drug Administration Staff; Design Considerations for Pivotal Clinical Investigations for Medical Devices* (“Draft Guidance”) and in particular, how the Draft Guidance impacts combination product research and policy development.

By way of background, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products arena. One of the principal goals of our organization is to work collaboratively with the Agency on issues affecting combination products, in order to advance our common missions of providing the best possible health care for patients. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

We are pleased the Draft Guidance acknowledges its applicability to combination products. We believe the next iteration of the guidance should expand upon this general statement of applicability and offer specific guidance on combination products with a device constituent part. The combination product industry has for years awaited guidance on clinical trials involving combination products. Specifically addressing combination products in this guidance would be an important step forward in combination product

policy development. Below, we provide general and specific comments on the guidance that is needed.

## 1. GENERAL COMMENTS

The combination product industry has long expressed a need for guidance in the clinical trials area. Early in 2008, the CPC conducted a survey of the combination product industry on the industry's top priorities for FDA guidance development. The topic of clinical trials was ranked as the number one priority. This topic has remained at the top of the CPC's own priority list for years. To advance these issues, the CPC developed and, in February 2009, submitted to the Agency a *Draft Guidance for Industry and FDA Staff: FAQs on Pre-Clinical and Clinical Research on Combination Products*. To date, we have not received feedback on this draft guidance.

The Draft Guidance states: “[T]his guidance includes principles that are applicable to the device specific issues for combination products ... (e.g., device-drug products; device-biological products).” However, the Draft Guidance does not articulate *which* principles apply to combination products and does not provide any details regarding *how* the principles may apply to combination products. Guidance should be added for identifying regulatory needs for a clinical study when a combination product is developed. FDA also should identify any differences between requirements for new drug/device combinations and new device/approved drug combinations.

As another general matter, the guidance does not address labeling, including labeling for combination products. This is important when conducting clinical studies for combination products with a device constituent part. One issue here is where labeling information belongs; for example, if the device should not be used in a specific patient population, should this information be placed in the Instructions for Use, the Package Insert, or both?

Issues pertaining to clinical trials of combination products are of great importance to patients, the CPC, and others in the combination product area. With this in mind, we request that in the next iteration of the guidance (whether another draft or a final version), the Agency provide details regarding which principles apply to combination products and how these principles apply. Our specific comments below provide *examples* of areas that merit attention; these are not intended to be considered an all-inclusive list.

## 2. SPECIFIC COMMENTS

First, based on the Draft Guidance and our own experience, it seems clear that when CDRH has primary jurisdiction *and* the combination product is subject to either a PMA or 510(k), then a clinical investigation conducted outside of the U.S. is required to comply with 21 C.F.R. Part 812. However, the Agency should clarify that when CDRH does not have primary jurisdiction over a combination product that includes a device constituent part, a clinical investigation conducted outside of the U.S. should not be *required* to comply with Part 812; rather, the principles for acceptance of the study data to

support a submission would be the same as in other areas, such as drugs. Additionally, in cases where the study will be used to support an NDA or BLA for a combination product, we believe that compliance with Part 812 should not be necessary when the sponsor is conducting the study under an IND. Although in some cases sponsors may choose to use a “hybrid” approach that combines requirements of Parts 312 and 812, the Agency should not mandate such an approach.

Another issue concerns whether and when an Investigational Device Exemption (“IDE”) is required for a clinical investigation of a combination product that includes a device constituent part. The Agency has provided guidance regarding whether a device is a significant risk device or a non-significant risk device. This guidance, however, does not squarely apply to combination products. For example, there may be instances where if the study of a device constituent part of a combination product is analyzed in isolation, that study does not pose a non-significant risk. However, where a combination product is concerned, often a premarket submission will be for the combination product as a whole. Here, the analysis may differ in terms of risk level. In these cases, the industry needs clarity on how to evaluate studies of combination products and their need for an IDE under 21 C.F.R. Part 812. We suggest that the Agency clarify that the focus should be on the risk of the *study*, not on the device or combination product in isolation. As with the issue described in the previous paragraph, the Agency also should clarify that an IDE generally is not needed when a sponsor holds an IND.

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Again, we commend the Agency for specifically recognizing that the Draft Guidance may apply to clinical investigations involving combination products that incorporate a device constituent part. However, the guidance needs additional guidance specific to such combination products, and we urge the Agency to include such information in the next iteration of the guidance.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Bradley Merrill Thompson', written in a cursive style.

Bradley Merrill Thompson,  
On behalf of the Combination Products Coalition

cc:

Jill Warner, Associate Commissioner (Acting), Office of Special Medical Programs  
Thinh Nguyen, Director, Office of Combination Products