Combination Products Coalition

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VIA ELECTRONIC SUBMISSION

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

Re: Comments to FDA Guidance:
Distinguishing Medical Device Recalls From
Product Enhancements; Reporting Requirements
Docket No. FDA-2013-D-0114

Dear Sir or Madam:

On behalf of the Combination Products Coalition ("CPC"), we welcome the opportunity to comment on FDA's Draft Guidance, *Distinguishing Medical Device Recalls From Product Enhancements; Reporting Requirements* (hereinafter, "Draft Guidance").

By way of background, the CPC is a diverse group of drug, biological product, and medical device manufacturers with substantial experience in the combination products area. Our members range in size from small start-ups to multi-billion dollar manufacturers. These companies all share an intense interest in policy issues affecting combination products. Because of our diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

One of our principal goals is to work with FDA on such issues in order to advance our common mission of providing the best possible health care for patients. In this regard, the CPC has had frequent dialogue with FDA on regulations, guidance documents, and other policy issues that affect combination products and how best to serve patient needs with respect to such products. For example, we have submitted dozens of written comments, policy documents, proposed guidance documents, and other materials to the agency on these issues for nearly a decade. If you are interested, you can find several of these materials on our website: http://www.combinationproducts.com/.

The Draft Guidance could have far reaching implications on device innovation, and on combination products that include device constituents. If a manufacturer believes a beneficial change to the device constituent of a combination product falls in a gray area where it considers the change an "enhancement" but believes FDA might call it a "recall," it creates a disincentive to making the change because the difference of opinion with FDA could result in a public pronouncement on the Agency's recall website that FDA considers the product to be violative.

As the CPC's principal goal is to address issues specific to combination products, our comments are not designed to address all issues with the Draft Guidance. To that end the CPC's comments seek to clarify the Draft Guidance's applicability to combination products. Additionally we suggest a few minor miscellaneous corrections/clarifications FDA should make if it develops a final guidance. However, our decision to limit our comments should not be interpreted as an endorsement of the Draft Guidance nor should the absence of a comment on a particular point be considered an endorsement of that point by the CPC. The draft guidance raises a number of important concerns, such as (a) the need for better clarification between enhancements and recalls, (b) whether FDA is expanding regulatory reporting requirements under 21 C.F.R. part 806 through a guidance document, and (c) whether some of the guidance on enhancements crosses into territory that is better reserved for the new guidance FDA is developing on premarket notifications following product changes. These are serious issues we expect others (including some CPC members) will comment on, and that we hope will be addressed fully by the Agency.

## I. Application of the Guidance to Combination Products

A combination product is comprised of two or more different regulated components (e.g., device/drug, device/biologic) that are combined into a single entity; co-packaged; or labeled in such a way that the two components must be used together.[1] As written, the Draft Guidance clearly applies to *devices*, discussing how to distinguish between device enhancements and device recalls, and whether an "806 report" is needed due to a reduced risk to health from a device. What is unclear is when and how the Draft Guidance applies to *combination products* with device constituents.

Assuming the Draft Guidance does apply, the Guidance should consider unique issues that arise with combination products. For example, the Draft Guidance states that a product enhancement is a change to a product that is "both (1) a change to improve the performance or quality of a device, and (2) *not* a change to remedy a violation of the Federal Food, Drug, and Cosmetic Act … caused by the device." With combination products, deciding whether these criteria are met is not always straightforward. For example:

A. For a drug eluting stent ("DES") what changes (if any) to the drug constituent would be considered an improvement to "the performance or quality of a device"?

B. If a device constituent is changed to help remedy a violation of the Act caused by a *drug* (not device) constituent, could that change still be considered an "enhancement" to the device constituent? As written, the Draft Guidance seems to say "yes."

Similarly, where questions arise about changes reducing risks to health and triggering 806 reportability requirements, the interrelationship of the drug and device can make it difficult to decide whether a safety issue is device-related and subject to the guidance. For example:

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[1] 21 C.F.R. § 3.2(e).

A. The overall safety of a DES is related both to the device (stent) and its drug constituents. If a safety warning related to adverse events with the drug constituent is added to the product labeling for the drug eluting stent, is the change subject to the guidance on reportability?

B. The overall safety of a drug administered with a pen injector relates to the drug itself and the injector. If the drug is reformulated to change an excipient and reduce the risk of adverse reactions, and a corresponding material change is made to the injector to avoid compatibility issues with the new formulation/excipient, is the change subject to the guidance on reportability?

Given these ambiguities, the CPC urges that any final guidance address whether and how it applies to combination products (with illustrative examples), giving consideration to the kinds of questions provided above. Further, we recommend that single-entity combination products which have drug or biologic primary modes of action be explicitly excluded from the guidance; these products are more appropriately regulated as drugs or biologics, and should not be subject to this guidance on device regulations.[2]

II. Miscellaneous Corrections and Clarifications

1. Lines 219-21

The Draft Guidance states:

> FDA generally considers devices that fail to meet specifications and devices that fail to perform as intended to be of a quality below what they purport or are represented to possess, which would render them adulterated under section 501(c) of the FD&C Act.

By its terms, section 501(c), which is entitled *Misrepresentation of strength, etc., where drug is unrecognized in compendium* (emphasis added), applies to non-compendium drugs, not devices. We therefore suggest replacing this language and the citation as follows:

> FDA generally considers devices that fail to (a) meet specifications developed under design controls or otherwise conform with Quality System requirements, or (b) conform with performance standards the manufacturer claims it meets, to be adulterated under sections 501(h) or (e) of the FD&C Act.

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[2] In this regard, the notice announcing the Draft Guidance stated that "The draft guidance, when finalized, will represent the agency's current thinking on the difference between a recall and an enhancement to an existing premarket approval application (PMA) or 510(k)." 78 Fed. Reg. 12329, 12330. If the intent is that this guidance will be limited to products with PMAs and 510(k)s, we suggest that a statement to that affect be added to the guidance. Also, we recommend clarifying if devices approved under BLAs would be subject to the guidance.

2. Lines 233-35

The Draft Guidance states:

> An increase in overall failure rate, increase in a single failure mode rate, or the identification of a new failure mode would indicate a failure to perform as intended.

Although increases in failure rates and identification of new failure modes *might* indicate a failure to perform as intended, whether they actually *would* do so depends on the facts. For example, a non-meaningful (e.g., non-significant, or statistically significant but inconsequential) increase in a failure rate does not indicate a failure to perform as intended. Similarly, a previously unidentified failure mode with an extremely low recurrence potential does not necessarily mean devices in the field are failing to perform as intended. Therefore, we recommend revising this sentence to read:

> A~~n~~ meaningful increase in overall failure rate~~, increase~~ or in a single failure mode rate, or the identification of a new failure mode ~~would~~ might indicate a failure to perform as intended.

3. Line 288

The reference to "807.10(f)" should be changed to "806.10(f)"

4. Lines 384-85

In discussing the Agency's method for evaluating risk, the Draft Guidance states "[t]he lack of reported injuries does not decrease the level of risk assigned." Although the lack of reported injuries does not always bear on the level of risk, in some cases that information can be relevant. In addition, with technological advances in communication (such as FDA's new mobile application for voluntary MDR reporting) and improved awareness by healthcare personnel that events should be reported to FDA and/or manufacturers, the absence of reported injuries should become even more pertinent in risk analyses in the future. Therefore, we suggest revising the statement to read: "The lack of reported injuries does not always decrease the level of risk assigned." The CPC also recommends the FDA routinely give at least some consideration to a lack of reported injuries in risk analyses for the reasons above.

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We appreciate the opportunity to comment on the Draft Guidance and hope these comments will allow the Agency to clarify points, particularly with respect to combination products, in any final guidance that is published.

Kindest regards,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition