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Re: Docket No. FDA-2012-D-1240; Comments on the FDA Draft Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved under a BLA, NDA or PMA.

Dear Sir or Madam:

The Combination Products Coalition ("CPC") is pleased to offer its comments on the Draft Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved under a BLA, NDA or PMA ("Draft Guidance"). Although this Draft Guidance appears narrow in scope and we request additional clarification, we commend FDA for taking the first step towards providing some clarity in the requirements applicable to postapproval changes to combination products. We are sympathetic to the challenges FDA likely has had in drafting guidance in this area as we understand that this area may be one of the most difficult and complex regulatory issues impacting combination products and that the Agency has reason to be cautious due to the recent controversies that arose when it attempted to improve the guidance on when a new premarket submission was required.

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.

Below we offer our comments on the Draft Guidance. We have general, overarching comments on the Draft Guidance as well as some specific comments. Overall, we are delighted to see the publication of this long anticipated Draft Guidance. However, it is unclear as to whether the guidance only addresses the type of submission that should be submitted if a manufacturer determines that a submission is required or also addresses how manufacturers should evaluate whether a submission is required. Additionally, to the extent the scope is limited to the former, the value of the guidance may be considered limited because it does not address

the types of submissions that would be required if a change was made to a device constituent part that would be subject to 510(k) rules, if it were a stand-alone device. The utility of the guidance is further limited by the exclusion of combination products marketed under a 510(k) or under multiple applications. Below we provide recommendations on the changes to improve the Draft Guidance and provide clarity regarding the requirements applicable to postapproval changes to combination products

I. **FDA should clarify and expand the scope of the Draft Guidance**

The Draft Guidance states that it is intended to "provide clarity in the postapproval change requirements and consistency in the type of post market submission to provide or a change to a combination product approved under one application." (Lines 67-70). Most, if not all of our members interpreted this to mean that the Draft Guidance was designed to provide additional insight into how to apply the "criteria to be used in determining when a postapproval submission is required" and assist manufacturers in determining the type of submission required. However, based on informal conversations with individuals from FDA we came away with the impression that their intent was to limit the scope of the Draft Guidance to the latter and is not intended to address the former.

As this intent is not clearly expressed in the guidance we recommend FDA take the following steps to improve the utility of the Draft Guidance:

1. Clarify that the guidance does not address which standards should be applied by manufacturers to determine whether a change to a constituent part would have required a postmarket submission, if it were a standalone product;
2. Expand the scope to include guidance on the types of submissions that are required if a change is made to a constituent part of any type of combination product, including those marketed under a 510(k); those with device constituent parts that, if standing alone, would be subject to 510(k) rules and those marketed under multiple applications

Additionally, FDA should develop guidance that addresses how companies should apply existing guidance to determine whether a change to a constituent part would require a postmarket submission, if it were a standalone product.

A. FDA should clarify the scope of the Draft Guidance

Although FDA intended for this guidance to only address the type of submission required, the information included in the Draft Guidance goes beyond this limited intent. In particular, the Draft Guidance lays out the following two factors for determining whether a change to a constituent part requires a postmarket submission:

1. "If a change is made to any constituent part of the combination product that would have required a postmarket submission to FDA if the constituent part were a stand-alone product, then a post market submission is required for the Combination Product."[1]
2. "A postmarket submission would also be required if a change to any of the constituent parts would otherwise trigger the requirements associated with the application type used for approval of the combination product."[2]

Further, the Draft Guidance states that the criteria for analyzing the submission requirements include whether a submission would ordinarily be required for the modification, if the constituent part were marketed as a stand-alone product. Specifically, the appropriate device criteria should be applied to device constituent parts,[3] drug criteria should apply to drug constituent parts and biologic product criteria should be applied to biologic constituent parts. Also, the Draft Guidance discusses the possibility that some changes to device constituent parts could result in the formation of a new combination product.[4]

Specifying when a submission is required, also appears to be included within the scope of the Draft Guidance. For instance, the second paragraph of Section II of the Draft Guidance directs the reader to the statutory and regulatory "provisions describing when a postmarket submission is required for a change to an approved stand-alone drug, device, or biologic product or its manufacturing process." (lines 60-62). The paragraph further describes the intent of the Draft Guidance as being "to provide clarity in the postapproval change requirements and consistency in the type of postmarket submission to provide for a change in the combination product approved under one application." (Lines 67-70). As this language refers to both the type of the application and the postapproval change requirements, it is easy to interpret this as intending to provide information on how to determine if a submission is required.

Additionally, the Draft Guidance fails to specifically exclude this from its scope. There are several sections of the Draft Guidance that include language specifically limiting its scope. However, none of these sections include language excluding "how to determine whether a submission is required." Rather this just limits the types of combination products to which this guidance is applicable and note that the Draft Guidance does not address the type and amount of information to be included in the submission.[5]

If FDA's intent is to exclude from the Draft Guidance how companies should evaluate whether a change requires a postapproval submission from the scope of this guidance, FDA should specifically state so. Additionally, FDA should delete the language that lays out when a postmarket submission is required and how companies should analyze whether a change triggers such a requirement.

[1] Lines 79-81
[2] Lines 82-84
[3] Although, the Draft Guidance only includes an analysis of a device constituent part that would be subject to PMA criteria if it were a stand-alone product, this language seems to contemplate that there are certain device constituent parts that would be subject to 510(k) rules if they were stand-alone products.
[4] See Footnote 20 of the Draft Guidance. See Section II.B. for additional discussion of this footnote.
[5] See Lines 25-32 ("This guidance does not address changes to combination products that are not approved under a BLA, NDA or PMA (e.g., those cleared solely under a device premarket notification submission or those marketed under an over-the-counter drug monograph).

B. The Guidance Document should address postmarket submission requirements for all combination products.

The Draft Guidance specifically excludes combination products marketed under a 510(k) pre-market notification, those marketed under an OTC monograph, and combination products marketed under multiple submissions. Further, the Guidance does not address the type of postmarket submission that would be required if a change was made to a device constituent part of a combination products approved under an NDA or BLA, if that device constituent part would have been subject to 510(k) rules, if it were a stand-alone device.

It is not clear to the CPC why FDA chose to exclude combination products marketed under certain procedural mechanisms. We understand that the excluded types of combination products may present issues that are more difficult to address than those raised by the types of combination products addressed in the Draft Guidance. However, it is for this reason that FDA should provide guidance in this area. We understand the agency's resources do not allow it to provide guidance on every topic Therefore, it is important that FDA expend its resources in areas where guidance is most needed.

With the exception of the mapping of NDA and BLA Prior Approval Supplements to PMA 180-day or Real Time Supplements, the mapping of an NDA or BLA postapproval submission to a PMA postapproval submission (and vice versa) is fairly self-explanatory. However, the postmarket submission requirements with respect to changes to the combination products that were specifically excluded from or not included in the Draft Guidance are not so clear. In particular with respect to combination products approved under more than one application, although the submission requirements are clear with respect to submissions related to the application for the constituent part that has been changed, there is no guidance regarding the submission requirements with respect to the application for the unchanged constituent part. For example, if a manufacturer makes a change to the device constituent part of a combination product with constituent parts approved under a PMA and NDA respectively, the submission requirements related to the PMA application will be governed by PMA rules. However, there is no guidance to assist in determining whether the change to the device constituent part requires submissions with respect to the NDA. Additionally, as discussed in more detail below in Section II.A, this guidance does not adequately address the types of submissions required if a change is made to the device constituent part of a combination product approved under an NDA or BLA, if the constituent part, standing alone, would be subject to 510(k) rules.

In order to make this a complete guidance on the type of submission required following a postmarket change to a constituent part, the final guidance should address the submission requirements for changes to combination products marketed under a 510(k), those marketed under more than one application, and those marketed under an NDA or BLA that contain a device constituent part that, if standing alone would be subject to 510(k) requirements.

II. FDA should develop guidance on how to apply existing regulations and guidance to determine whether a postmarket change to a constituent part triggers the need to make a postmarket submission and whether such a change results in a new combination product

FDA has developed extensive guidance providing examples of the types of changes that will trigger the need for a postmarket submission, with respect to standalone products submitted under an NDA, BLA, 510(k) or PMA.[6] However, none of these guidance documents specifically address whether the analysis is similar with respect to combination product constituent parts. Therefore, as the Draft Guidance is not intended to address this issue, we request FDA issue such guidance.

A. FDA Guidance addressing whether a postmarket submission is required due to a change in a constituent part should ensure that the requirements applicable to changes to a constituent part are similar to similar standalone products.

The Draft Guidance states that manufacturers should "apply the appropriate device criteria in determining what would ordinarily have been submitted because of the change to the device constituent part… and [f]or a biological product or drug constituent, apply the appropriate biological product or drug criteria, respectively." As there is only one set of criteria applicable to drugs and one for biological products, it is not difficult to determine which criteria are applicable to each. However, as there are two sets of criteria for device constituent parts, PMA criteria and 510(k) criteria, the first step in the analysis is determining which set of criteria apply.

The Draft Guidance fails to recognize this as a critical distinction. If there is a similar stand-alone device on the market, the rules governing that device should apply to the constituent part. If there is no similar stand-alone device on the market and there is no predicate device to which the constituent part could be substantially equivalent then PMA rules should apply. However, we understand that FDA may have concerns with the application of 510(k) requirements to some device constituent parts because of their inclusion in a combination product.

We understand FDA's concerns that a combination product is not just the sum of its constituent parts. However, we believe treating device constituent parts differently than similar standalone devices would be contrary to Congressional intent with respect to devices subject to 510(k) premarket notification.[7] Specifically, Congress' intent that FDA look for ways to

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[6] See e.g., FDA Guidance for *Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process* (2008), at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf; FDA Guidance for *Changes to an Approved NDA or ANDA* (2004), at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm077097.pdf; FDA Guidance for *Changes to an Approved Application: Biological Products* (1997), at http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM170166.pdf.

[7] Pursuant to Section 604 of the Food and Drug Administration Safety and Innovation Act (FDASIA) not only was FDA required to withdraw the draft guidance issued on July 27, 2011entitled "510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device," FDA was prohibited from issuing a new

facilitate continual device improvement. Additionally, we believe that the existing regulatory framework is sufficient to address these concerns and there is no need to subject all device constituent parts to PMA rules.

Applying PMA requirements to all device constituent parts will likely increase the number of postmarket submission requiring prior approval and thus likely will inhibit innovation. The significant increase in submissions will happen because the trigger for PMA supplements is "significantly" lower than the trigger for when a change requires a new 510(k) to be submitted.[8] Specifically, the PMA rules require a supplement to be file if the change "affects the safety or effectiveness of the device."[9] Whereas, the 510(k) rules only require a new 510(k) to be submitted if the change "could significantly affect the safety or effectiveness of the device."[10]

To illustrate this point, two examples are given:

1. A pharmaceutical manufacturer files an NDA supplement to include an autoinjector. The autoinjector, if it was a stand-alone device, would be subject to 510(k) premarket notification, not a PMA. If the manufacturer decides to manufacture the autoinjector at a new facility, unless it determines that the change in manufacturing facilities could significantly affect the safety or effectiveness of the device, then no submission would be required, under 510(k) rules. However, under the PMA rules, a postapproval submission would be required and FDA would need to approve the change prior to distributing the combination product that incorporates the autoinjector that was manufactured at the new facility.[11] Further, the burden of the submission may be greater than would be required if the pharmaceutical manufacturer decided to manufacturer the drug substance at a different site.[12]

2. The supplier of components of the autoinjector makes a change in the vendor of a raw material or changes a material being supplied to a specification. Under the 510(k) rules, submission of a 510(k) is probably not necessary.[13] However, if the

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guidance on this topic until it submits a report to Congress addressing ways FDA can utilize existing quality systems to facilitate continual device improvement and reduce pre-market burden.

[8] Ultimately the decision a manufacturer must make, is whether the change results in the product no longer being within the design specifications and manufacturing description in the approved or cleared marketing application or submission. However, the regulations applicable to each provide a standard against which the manufacturer is required to measure the change.

[9] 21 CFR § 814.39(a)

[10] 21 CFR § 807.81(a)(3)(i)

[11] 21 CFR § 814.39(a)(3); *See also* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm051387.htm#8

[12] According to the Draft Guidance, the device constituent part change would require a Prior Approval Supplement to be filed, whereas the drug substance change would only require a Supplement-Changes Being Effected in 30 days (*See* FDA, Guidance for Industry – Changes to an Approved NDA or ANDA VI.B.1.b at 10.)

[13] Reference "Deciding When to Submit a 510(k) for a Change to an Existing Device (K97-1)" issued January 10, 1997 (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm).

> autoinjector is subject to PMA rules, such a change in vendor or materials may trigger the need for some sort of PMA supplement. Therefore, these fairly innocuous changes would get reviewed from the standpoint of what triggers a PMA supplement, however, from a risk assessment perspective, the change in vendor or material would likely not trigger the need for a new submission under the premarket notification rules.

The CPC agrees with FDA that in many cases it will not be difficult for a manufacturer to isolate a change to one constituent part from the other constituent part. There also may be times where a manufacturer can validate that a change to one constituent part will not impact the other constituent part. Therefore, if a manufacturer has validated that a change to one constituent part does not impact the other constituent part, the manufacturer should not be required to analyze the impact of such a change to the other constituent part. For example, a manufacturer has previously evaluated the impact of a drug product manufacturing site change and demonstrated that such a change does not impact the drug product quality either standing alone or as used in the autoinjector. If the manufacturer makes a subsequent manufacturing site change, and the manufacturer determines the change does not impact the drug product quality standing alone, it should not be required to determine if the change impacts the drug product quality as used in the autoinjector.

We also recognize that there may be additional safety and efficacy concerns associated with pre-filled injector systems beyond those associated with the injector-system itself, such as long-term biocompatibility and compatibility between the injector system components and the filled drug or biologic. When appropriate, a change to a device constituent part will not only be analyzed under the rules applicable to the device constituent part, it will be analyzed under the rules applicable to the other constituent part; the drug or biological product constituent part. For example, if the device constituent part serves as a container closure system for the drug constituent part, any change would be analyzed under the rules and guidance applicable to changes to drug product container closures. FDA has already developed guidance in this area that appears to contemplate how to analyze a change to a device constituent part that serves as a drug's container closure. Additionally, even if the device constituent part does not serve as the drug's container closure, the change will still need to be analyzed not only for its impact on the device constituent part but on the combination product as a whole. This analysis will be done under the rule applicable to the submission type of the changed constituent part if it was a stand-alone product and under the submission type by which the combination product was approved.

Therefore, when FDA issues guidance on how to analyze whether a submission is required due to a postmarket change, the guidance should be clear that a change to a device constituent part that would be subject to 510(k) regulations, if it were a stand-alone device, should be analyzed using the 510(k) requirements. The guidance should also be clear that this does not mean that the change should not be analyzed under other applicable criteria or that the change's impact on the product as a whole should not be analyzed using the criteria applicable to the combination product.

B. The Agency should clarify when a change to a constituent part results in a new combination product

Footnote 20 states that "[i]n some instances, the change in the device constituent part may result in a new combination product." However, the Draft Guidance does not provide any additional detail regarding when such instances may occur, nor does it seem to imply that certain changes to drug or biological product constituent part could result in a new combination product. It seems unlikely that the Agency believes that only changes to the device constituent part can result in a new combination product, but the CPC requests clarity in such a situation.

We ask the agency to either delete this footnote or clarify what changes to a constituent part will result in a new combination product.

Kindest Regards,

Bradley Merrill Thompson,
On behalf of the Combination Products Coalition