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VIA ELECTRONIC SUBMISSION

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

Re: Premarket Notification Requirements for Modifications to Legally Marketed Devices; Docket No. FDA-2014-N-0237-0001

Dear Sir or Madam:

On behalf of the Combination Products Coalition (“CPC”),¹ we welcome the opportunity to offer comments on the recent “Report on FDA’s Policy to be Proposed Regarding Premarket Notification Requirements for Modifications to Legally Marketed Devices.” The CPC appreciates this first step towards developing more comprehensive guidance and clarifying when a manufacturer is required to submit a 510(k) notification for a modification to a marketed device, specifically FDA’s commitment to use the 1997 guidance as the starting point. However, with respect to combination products, more than clarification of the 1997 guidance is necessary. If FDA only were to clarify certain aspects of the 1997 guidance, combination product manufacturers would be left exactly where they are today, without guidance on when a post-market submission is required when a change is made to a combination product marketed under a 510(k) or a combination product device constituent part that, if standing alone, would be regulated as a class II device (moderate to low risk based on the level of control necessary to assure the safety and effectiveness of the device) and therefore marketed under a 510(k). Device constituent parts in this second category will be referred to as “class II equivalent constituent

¹ The CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in combination product issues. One of our top priorities is to work collaboratively with FDA on issues affecting combination products to advance our common mission: providing the best possible health care to patients. Our diverse, cross-industry membership permits the CPC to bring a special, broad and unique perspective to these issues.

parts” in this document to the extent they are incorporated into combination products approved under NDAs or BLAs.²

Understanding when a post-market submission is required is no less important to combination product manufacturers than it is to medical device manufacturers or drug manufacturers. However, combination product manufacturers have little, if any, formal guidance to help them understand how to analyze whether a post-market submission is required if they make a change to a combination product marketed under a 510(k) or to a class II equivalent constituent part. Although there are significantly fewer combination products marketed under 510(k)s than there are marketed under PMAs, hundreds of such combination products have been cleared in the last decade.³ Therefore, we request FDA ensure the updated guidance expressly applies to combination products marketed pursuant to 510(k) clearance.

In addition to ensuring the updated guidance applies to combination products marketed under 510(k)s, the CPC asks that FDA ensure this updated guidance will be applicable to changes to class II equivalent constituent parts. According to the Draft *Guidance for Industry and FDA Staff: Submissions for Postapproval Modifications to a Combination Product Approved Under a BLA, NDA or PMA*, (“OCP Draft Guidance”), constituent parts of a combination product retain their regulatory identity as a drug, device or biological product. Therefore, if a change is made to any constituent part of the combination product that would have required a postmarket submission if the constituent part were a stand-alone product, then a postmarket submission is required for the combination product. In this guidance, combination product manufacturers are instructed to analyze a change to a constituent part, by evaluating the change using the criteria that would be applicable if the constituent part were a stand-alone product. Therefore, one would think that combination product manufacturers with class II equivalent device constituent parts (e.g., pen injector) should be able to analyze changes using the criteria used to determine if a new 510(k) submission is required. However, the OCP Draft Guidance only provides examples using the criteria for analyzing the type of PMA supplement that may be required in the event of a change to a device constituent part, with no reference to the retention of its class II equivalent identity.

² We acknowledge that FDA recently issued a proposed rule that would “up-classify” (i.e., regulate as a Class III device) a combination product with a device primary mode of action that consists of a Class I (low-risk) or a Class II (moderate-risk) device combined with an unapproved drug or biologic. *See* Medical Device Classification Procedures, 79 Fed. Reg. 16, 252 (Proposed Mar. 25, 2014) (to be codified at 21 C.F.R. pt. 860). Also, we recognize, that this proposed rule may not need to be finalized before FDA can regulate such a combination product as a Class III device because, if such a combination product were subject only to premarket clearance, FDA may be exceeding its authority by subjecting an unapproved drug or biologic only to premarket clearance and not premarket approval. However, such “up-classification” is not required with respect to Class II equivalent device constituent parts because the combination products into which they are incorporated would be approved and FDA has the authority to permit certain low-risk and moderate-risk devices to be marketed pursuant to a clearance.

³ A search of combination products in the FDA 510(k) database on May 5, 2014 resulted in 500 entries dating back to March 2005, whereas a search of combination products in the FDA PMA database resulted in 500 entries dating back to September 2012.

Additionally, in other circumstances, FDA has instructed our members to apply additional requirements that generally apply to class III, high risk devices (e.g., clinical investigations, benefit-risk determinations, submission of quality system procedures) to combination products with class II equivalent device constituent parts. Combined, these directions from different sources have caused our members to question whether the criteria for determining if a new 510(k) submission is required should be used to evaluate changes to class II equivalent device constituent parts. Therefore, we request that FDA clarify its position by clearly stating that the draft guidance applies to changes to class II equivalent device constituent parts.⁴

In addition to clarifying this ambiguity, such a statement will “ensure the consistency and appropriateness of post-market regulation of like products” in accordance with Section 503(g)(4)(D) of the FD&C Act. We recognize that there are different risks that must be analyzed when reviewing a change to a standalone device as opposed to a change to a device constituent part. However, these risks are already addressed because a post-market submission would be required if the change to the constituent part would otherwise trigger the requirements under the NDA or BLA. For the most part, even if a manufacturer analyzes a change under the 510(k) criteria and determines that a new 510(k) is not required, unless the change is so minor that it does not have even minimal potential to have an adverse effect on the drug product, the change will at least be reported in the manufacturer’s annual report.⁵

Therefore, to ensure the updated guidance expressly applies to combination products and provides for consistent and equivalent treatment of finished devices and device constituent parts, the CPC recommends that FDA (1) expressly declare the applicability of the guidance to (a) combination products marketed pursuant to 510(k) clearance and (b) class II equivalent device constituent parts; and (2) include specific examples involving modifications to combination products to which the guidance applies.

⁴ We acknowledge that doing so may raise difficulties in mapping the binary submission requirements applicable to 510(k)s with the multiple choice submission requirements applicable to NDAs and BLAs. However, this mapping can be addressed in an updated version of the OCP Draft Guidance.

⁵ 21 C.F.R. § 314.70(d) (2014). Additionally, to the extent the device constituent part is also the drug product’s container closure, most changes to the device constituent part are likely to at least require notification pursuant to changes being effected in 30 days in a supplement submission pursuant to 21 C.F.R. § 314.70(c)(2)(i), and some may require a prior approval supplement pursuant to 21 C.F.R. § 314.70(b)(2)(iv).

We hope our comments are helpful to the Agency as it develops this guidance. If the CPC can help in any way, please do not hesitate to contact us.

Yours truly,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is written in a cursive style with a large, stylized initial "B".

Bradley Merrill Thompson