



CPC COMBINATION PRODUCT COALITION

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Comments on Draft Guidance for Industry and FDA Staff: Application User Fees for Combination Products; Docket Number 2004D-0410

Dear Sir or Madam:

The Combination Products Coalition ("CPC") respectfully submits these comments on the draft *Guidance for Industry and FDA Staff: Application User Fees for Combination Products* ("User Fee Guidance") published by the Food and Drug Administration ("FDA") in September 2004. The CPC is a group of leading drug, device and biologics manufacturers with substantial experience and interest in the combination products arena, as well as in each of the constituent technologies. Because of its diverse cross-industry membership, the CPC brings a uniquely broad combination product perspective to the regulation of such products. From that perspective, we offer the following comments.

I. General Comments

As a general matter, we commend the FDA for its efforts to bring definition and structure to the regulation of combination products. In particular, we compliment FDA on the transparent process that the agency has adopted as it formulates and clarifies regulatory policies affecting combination products. We strongly believe that such open interaction between FDA and stakeholders is critical to the development of sound regulatory policy. We encourage FDA to continue down this interactive path.

More specifically, we appreciate FDA's efforts in tackling the difficult issue of user fees for combination products. We believe the User Fee Guidance offers a good start, and we concur with its overall structure.

However, the User Fee Guidance raises a critical overarching policy issue that FDA needs to address before going any further: What regulatory scheme will FDA apply to a combination product, and on what basis will the agency make that determination? As discussed in the CPC's *Response to Request for Comment on Primary Mode of Action* filed with the FDA on August 18, 2004,¹ we are concerned that FDA might intend for the Primary Mode of Action to drive determination of not only which agency component will review a given combination product, but also which regulatory authorities will apply downstream. The User Fee Guidance, which ties user fees to the type of application and review, suggests that FDA indeed may be adopting such an approach. We caution against that far-reaching policy position. From the User Fee standpoint, such an interpretation has practical and economic consequences for combination products manufacturers that could impact their willingness to bring forth new and innovative products. On a broader scale, it could have tremendous implications on everything from registration to post-market reporting -- implications that could have an unfavorable impact on public health. For all of these reasons, we urge FDA to clarify its position regarding what regulatory scheme will apply to combination products. As FDA does so, we encourage the agency to consider the complexities of the downstream issues arising with combination products, and to ensure the type of flexibility and collaboration that such complexity demands.

In addition to this overarching concern, we think the User Fee Guidance could be strengthened by ensuring that the guidance better accommodates the tremendous diversity and novelty of combination products. While the User Fee Guidance acknowledges the diverse character of combination products by enumerating the different types of products included in the regulatory definition of combination products,² the guidance does not fully address the issues raised by these different types of products. In fact, the User Fee Guidance does a good job addressing fee issues raised by those products that are "physically, chemically, or otherwise combined or mixed and produced as a single entity"³ ("integral combination products"), but as explained below, it struggles with the challenges raised by separate products packaged together as "kits" and products not packaged as a unit but required to be used together to achieve the intended use, indication or effect ("virtual combination products"). With that in mind, we provide the following specific comments.

II. Specific Comments

A. Multiple Filings

We agree with FDA that, under certain circumstances, filing of multiple applications for a combination product may make sense. In addition, we are encouraged that FDA is preparing guidance that will define when multiple marketing applications should be

¹ (Letter from Bradley Merrill Thompson, Combination Products Coalition, to FDA of August 18, 2004, regarding Response to Request for Comment on Primary Mode of Action, Food and Drug Administration Docket Number 2004N-0194)

² See FDA, *Draft Guidance for Industry and FDA Staff: Application User Fees for Combination Products* 4 (September 2004).

³ See 21 CFR § 3.2(e) (defining combination product).

submitted by a manufacturer. Such clarification is critical to ensuring consistency and predictability within the combination products program.

As discussed in greater detail below, however, we are concerned that the User Fee Guidance, as currently written, could unfavorably impact the development of innovative combination products, particularly kit combination and virtual combination products. Although FDA has not yet provided criteria for when multiple applications and fees might be required, the nature of kits and virtual combination products, which may have separable components, are much more susceptible to multiple applications than their integral combination counterparts. As the agency has recognized, the assessment of multiple fees could represent a significant barrier to their development.⁴

Moreover, from a policy standpoint, we do not believe that the assessment of full, multiple fees for combination product submissions makes sense. The entire foundation of the user fee legislation is predicated on covering the costs of the resources needed for review of drugs, biologics and devices. When a review involves combination product components, the agency centers involved will review common scientific issues, indications, and supporting data. The commonalities in the applications will enable FDA to collaborate on the review, building speed and efficiencies into the review process and reducing the resources and time needed for the review. Some reduction in fees when a combination product is submitted through multiple applications makes sense.

With that in mind, we make the following specific recommendations.

1. Automatic Waiver for FDA-Required Multiple Applications

We believe that when FDA requires multiple applications for a combination product, the agency should *automatically* waive at least a portion of the user fees. Although it is not yet clear when and for what reasons FDA will require multiple applications, we assume that FDA will do so when the agency believes it will somehow enhance review or regulation of the product. Given that assumption, we believe automatic waiver makes sense, for two reasons. First, as discussed above, when a review involves combination products, the review carries inherent efficiencies that reduce the resources required to review that product. Second, FDA has consistently acknowledged that high user fees deter innovative development. That may be particularly the case when the fees are multiplied at the agency's behest, rather than by a manufacturer's choice. Because such deterrence to development could have a significant impact on the public health, we recommend that FDA consider an automatic waiver when the agency mandates multiple applications.

2. Access to Waivers for All Multiple-Application, Combination Product Submissions

We believe that the User Fee Guidance should provide access to waivers regardless of whether a decision to file multiple applications is made by FDA or a manufacturer. The resources needed to review multiple applications for a combination product do not vary depending on who initiates the multiple-application filing, or who gains from it. Indeed, whether

⁴ See *User Fee Guidance* at 8.

the FDA or a manufacturer initiates the filing of multiple applications, the same resources will be employed. As explained above, in both cases the review of multiple applications will take fewer resources than review of the same number of applications for separate, unrelated products.

Unfortunately, unlike combination products for which FDA demands multiple filings, under the User Fee Guidance, combination products for which a manufacturer chooses to file separate applications currently are foreclosed from the innovative combination product waiver.⁵ That leaves manufacturers with severely limited options to reduce their fees. Manufacturers, for example, can still seek waivers under PDUFA or the Medical Device User Fee & Modernization Act ("MDUFMA"), but presumably must do so based on each separate component of the product, rather than the combination product as a whole. The opportunity for exemption or waivers of device fees under MDUFMA is particularly limited.

Given the identical review issues raised by the filing of multiple applications initiated by FDA and manufacturers, they should be subject to similar treatment under the User Fee Guidance waivers. With that in mind, we urge FDA to open access to waivers for all multiple-application submissions of combination products, regardless of who determines that more than one application is needed.

C. Innovative Combination Product

We agree with FDA's concept of an "Innovative Combination Product" waiver. However, we believe that the criteria for obtaining the waiver raises issues that need to be addressed before a final guidance document is issued.

1. Eligibility Criteria

In addition to expanding the innovative combination product waiver to include products for which a manufacturer chooses to file separate applications (as discussed above), we recommend that FDA reconsider excluding from the waiver certain combination products with components that may have another use. As currently drafted, the User Fee Guidance does not apply to combination products that have components that can be used independently, except when FDA requires multiple applications. Instead, the waiver requires that the "two components of the product are specifically intended and labeled only for use together."⁶ Consequently, if one component of a combination product has already been approved and labeled for another use, the waiver will not apply -- even if the combination product offers tremendous public health advantages. For instance:

- A CYP450 test is potentially useful for determining a person's ability to metabolize certain drugs. None are currently approved. It is expected that a new 510(k) will be required for each new class of drugs indicated (e.g. cardiac drugs, renal drugs, psychiatric drugs, etc). Suppose the CYP450 obtains a 510(k), and is indicated for use in patients taking cardiac drugs. Later, a drug manufacturer determines that their cancer drug can only be used safely in conjunction with a CYP450 test. The CYP450 test would then be required to obtain a new 510(k) for that indication.

⁵ See *id.* at 9 (limiting eligibility for "Innovative Combination Product" waivers to those products for which FDA is *requiring* two fee-eligible marketing applications for the combination product).

⁶ See *id.*

Exclusion of such innovative products simply because one component may have an independent use unnecessarily burdens manufacturers, and deters development of products that benefit the public health.

2. Requirement of a Clinical Benefit

We also recommend that the Innovative Combination Product Waiver apply to user fees for significant innovations that bring advantages outside the clinical realm. The guidance currently focuses only on products that fulfill an unmet medical need, and identifies two pathways for making such a showing -- both of which have a clinical bias:⁷

- **No alternative treatment or means of diagnosis exists.** The emphasis on products for which no alternative treatment or means of diagnosis is available suggests that FDA's focus may be on life-saving technologies. This approach, however, could eliminate potential waivers for a wide range of innovative combination products for which an alternative treatment or means of diagnosis may be available -- unless the combination product meets the second, "clinically meaningful advantage" criteria.
- **Combination product offers significant, clinically meaningful benefit.** This requirement of a net clinical benefit precludes waivers for significant innovations that offer meaningful advantages to the healthcare community. Not all innovative combination products are designed to offer significant, clinically meaningful advantages. Instead, they may be designed to do things better, faster, easier, or in a more convenient way -- all of which can offer significant and meaningful advantages to public health. For instance:
 - A drug/device combination that combined an innovative, easy-to-use injection device with an injectable drug for home use would provide a usability benefit. Without a clinical benefit, it would be foreclosed from combination product consisting of a drug and device

For these reasons, we recommend that FDA remove the term "clinically" from the second criteria, and expand its consideration to innovations that lead to other significant, meaningful advantages -- such as economics, convenience and usability.

III. Conclusion

The CPC supports FDA's continuing efforts to shape and clarify the regulatory environment for combination products, and looks forward to working with the FDA to that end. We appreciate FDA's attention to user fee issues, and generally agree with the principles described in the User Fee Guidance. However, we believe that combination products offer unique challenges in this area. For that reason, we encourage FDA to consider these comments and revise the User Fee Guidance to better accommodate innovative combination products.

⁷ *Id.* at 10.

We appreciate the opportunity to share our thoughts with you, and look forward to working with you to resolve the issues raised here.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Bradley Merrill Thompson". The signature is written in a cursive style with some loops and flourishes.

Bradley Merrill Thompson