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November 29, 2004

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

**Re: *Docket Number 2004D-0410 - Comments on Draft Guidance for Industry and FDA Staff: Application User Fees for Combination Products***

Dear Sir or Madam:

AdvaMed, the Advanced Medical Technology Association, respectfully submits these comments to the Food and Drug Administration ("FDA") in response to a September 28, 2004 notice requesting comments on the Agency's draft guidance document *Guidance for Industry and FDA Staff: Application User Fees for Combination Products* ("User Fee Guidance").

AdvaMed represents more than 1,300 innovators and manufacturers of medical devices, diagnostic products and medical information systems. Its members produce nearly 90 percent of the \$75 billion in health technology products consumed yearly in the United States and nearly 50 percent of the \$175 billion purchased around the world annually. AdvaMed members range from the largest to the smallest medical technology innovators and companies. Nearly 70 percent of our members have fewer than \$30 million in sales annually. A significant and growing percentage of our member companies have health care products that incorporate combination technology, the subject of FDA's request for comments.

#### **GENERAL COMMENTS**

We commend the FDA for its efforts to bring clarity to the difficult issue of the application of user fees to combination products. The wide variety in the types and complexities of combination products makes the application of user fees a very important concern for manufacturers. While the User Fee Guidance is good first step in that effort, it

does not completely address all the issues raised by this complex product area. Guidance on when multiple marketing applications should be submitted would help provide manufacturers some assurance of consistency and predictability within the combination products program.

## **SPECIFIC COMMENTS**

### **I. Multiple Application**

Manufacturers of combination products often file multiple applications for a combination product. While the User Fee Guidance describes how the “barrier to innovation” waiver provision under the prescription drug user fee provisions of the Federal Food, Drug, and Cosmetic Act (the Act) may be applied to innovative combination products for which FDA requires the submission of two applications, it may also restrict the availability of waivers for certain innovative combination products for which multiple applications are filed and for which FDA has not required the submission of multiple applications.

Use of the Prescription Drug User Fee Act (PDUFA) "barrier to innovation" waiver provision in the case of two applications for a combination product is appropriate. However, we disagree with limiting this provision only to those situations in which FDA requires two applications. A sponsor who chooses to submit two applications to avail himself of some benefit of having two applications, such as proprietary data protection or orphan status should also be allowed to avail himself of the benefit provided under the PDUFA "barrier to innovation" waiver.

Combination products incorporating cutting edge, innovative technologies submitted under two applications do not contain any more data or information than when submitted under a single application where consultation with another Center is a necessary component of the submission review. Regardless of who decides that two separate applications represent the most appropriate regulatory approach, eligibility for waivers should be the same. The decision to grant a waiver should be based on the innovative merits of the product, not which party determined that submission of two applications is appropriate for the combination product. We recommend a more flexible approach that is not based on whether the agency requires multiple submissions.

### **II. Review Burden**

The Agency should exercise flexibility in assessing User Fees for combination products, and consider not only whether one or two applications are required, but also the

review burden on the Agency. The collaborative review process may be essentially the same whether one or two applications are submitted.<sup>1</sup>

For example, for combination products such as drug-delivery devices that require two applications covering the separate components (e.g., a drug NDA and a device PMA or PMA supplement), the Agency historically has employed a collaborative review process similar to the process applicable to single applications. CDRH reviewed device-related issues and device labeling changes required to be mutually conforming to the new drug indication. CDER reviewed the safety and efficacy issues that were related to the drug and established by clinical data submitted to the NDA. In such situations, where one Center performs the majority of the data review, we propose that the application fee for the secondary application (e.g. PMA supplement) be significantly reduced to reflect the amount of resources expended for the secondary application.

This can be accomplished by aligning the type of marketing application to the expected review issues. For example, approval of a new drug for delivery by an approved delivery system would require an NDA for the new drug and a PMA supplement to add the drug to the delivery system labeling. While the PMA supplement technically may expand the delivery system indications for use, the Agency may categorize the PMA supplement as either a 180-day supplement or a real time review PMA supplement, rather than as a panel-track PMA supplement, as the clinical data is primarily reviewed under the NDA, and a PMA advisory panel review is not necessary. Flexibility in aligning the market application category with the Agency review resource requirements may reduce the number of waiver requests and result in a more equitable allocation of fees. AdvaMed suggests that the Agency and sponsor reach agreement on the appropriate category early in the process, either as part of the Request for Designation or in a pre-marketing submission meeting

### **III. Eligibility Criteria**

The User Fee Guidance states that the waiver would apply “when the two components of the product are specifically intended and labeled only for use together” (lines 259-264). It appears the intent of this provision is to avoid fee waivers where the combination product use is just one part of the marketing application. However, the proposed language could be an obstacle to legitimate fee waiver requests. For example, drug-delivery devices may be labeled for delivery of more than one drug. A strict reading of the first sentence would suggest that a fee waiver would not be appropriate where both an NDA and a PMA are required to approve a new drug/biologic and to add it to the device label, as the device would not be labeled solely for use with that drug. A fee waiver could be appropriate, if other conditions were met. We suggest that the first sentence in the bullet

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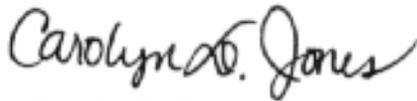
<sup>1</sup> Intercenter Consultive/Collaborative Review Process, Version 4, dated June 18, 2004, Manual of Standard Operating Procedures and Policies, <http://www.fda.gov/oc/ombudsman/intercentersop.pdf>, accessed November 23, 2004.

**Docket Number 2004D-0410**  
**November 29, 2004**  
**Page 4 of 4**

beginning on line 259 be replaced with the following language: *The marketing application for each component includes only indications that require use of the other.* The remainder of that paragraph should not change.

We appreciate the opportunity to share our concerns with FDA and look forward to working with the Agency to address issues related to its combination products program.

Respectfully submitted,

A handwritten signature in cursive script that reads "Carolyn D. Jones".

Carolyn D. Jones  
Associate Vice-President  
Technology and Regulatory Affairs