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

**Re: Docket No. 2005N-0098: Combination Products and Cross-Labeling**

Dear Sir or Madam:

AdvaMed respectfully provides this submission in response to the Food and Drug Administration's ("FDA's") March 28, 2005 request for comments and proposals concerning cross-labeling for combination technologies.<sup>1</sup> AdvaMed, the Advanced Medical Technology Association, represents more than 1,200 innovators and manufacturers of medical devices, diagnostic products and medical information systems. Its members produce nearly 90% of the \$75 billion in health technology products consumed yearly in the United States and nearly 50% of the \$175 billion purchased around the world annually. Member companies range from the largest to the smallest of technology innovators -- nearly 70 percent of our innovators have less than \$30 million in annual sales. Over the years, AdvaMed member companies have assumed a key role in developing many of the novel combination technologies currently on the market and under development. Our companies, thus, have a significant and vested interest in FDA's cross-labeling policies affecting this important category of products.

### **Executive Summary**

This submission provides AdvaMed's comments and proposals concerning cross-labeling for combination technologies, in response to the Food and Drug Administration's ("FDA's") March 28, 2005 Federal Register notice. Consistent with that Federal Register notice, our comments on cross-labeling are limited to the scenario offered -- separately packaged combination technologies involving non-cooperating entities. The essential elements and

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<sup>1</sup> 70 Fed. Reg. 15633 (Mar. 28, 2005).

principles that should guide solutions to this scenario, as outlined in the attached submission, are briefly summarized below.

- Guiding Principles: AdvaMed believes that three overarching principles -- optimal flexibility, fairness, and sound science -- should guide, and serve as the framework for, cross-labeling solutions, under the scenario presented.
- Authority Exists to Permit Flexible Cross-Labeling Solutions: Existing statutory authority and its legislative history support that:
  - (1) Congress established a fourth and distinct category of FDA-regulated products when it enacted combination-related provisions of law;
  - (2) Congress granted FDA authority to create unique solutions for this category of regulated products, that would avoid barriers to, and foster, innovation; and
  - (3) this flexible authority extends not simply to “combination products,” but to the broader category of “combination technologies,” even if those technologies ultimately are reviewed under device authorities.

Given this existing authority, a new regulatory paradigm is not needed to resolve the cross-labeling issues identified by the FDA.

- Definitions: New definitions are critical to refining the framework for cross-labeling solutions. In recognition that terms help guide solutions, AdvaMed has proposed definitions for such terms as: “combination technology;” “separately packaged combination technology;” “individually specified” products; “not individually specified” products; “branded/proprietary products;” “cross-labeling;” and “generally consistent labeling.” These definitions are provided at Attachment 2. The term “cross-labeling,” which AdvaMed has chosen to use rather than “mutually conforming,” is a particularly important definition, in that it provides the primary analysis for decisionmaking in this area.
- Framework for Cross-Labeling Determinations: AdvaMed proposes that determinations regarding the need for cross-labeling (and the related issue of conformance of drug and device labeling) be determined by its proposed definitions of “cross-labeling” and “general consistency.” AdvaMed’s proposed definitions build on the definition of “combination products” at 21 C.F.R. § 3.2(e)(3) and labeling principles of the Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (“ICA”). Under AdvaMed’s proposed definition of “cross-labeling,” cross-labeling will not be required if the combination technology does not “individually specify” a drug, and/or there is “general consistency” of indications, mode of delivery, and drug dosage/dosing schedule.

When “cross-labeling” is triggered, both Company A and Company B must modify labeling. Modifications to labeling will occur through premarket review of the

separately packaged products as a combination product, subject to primary mode of action analysis.

Conversely, cross-labeling will not be needed when an approved product is not individually specified and/or there is general consistency of indications, mode of delivery, and drug dosage/dosing schedule. In this case, only Company B's labeling would need to address use of the drug and device together, and the primary mode of action analysis for combination products will not apply.

In considering whether labeling is "generally consistent," labeling should be "similar" but need not be "identical," with respect to indications, mode of delivery, and drug dosage/dosing schedule. Additionally, even if there are inconsistencies in these three drug parameters, differences can still produce generally consistent labeling, if they can be addressed through a systematic risk analysis as part of the device company's risk management plan. Specifically, if the results of a risk analysis indicate that: (a) there are no issues with regard to safety and effectiveness that cannot be adequately addressed in Company B's labeling; and/or (b) the risks identified can be adequately mitigated by Company B's risk management plan, the differences should be permitted to be addressed in device labeling alone. As a final aspect to the term, "generally consistent labeling," there need not be consistency of secondary aspects of drug labeling (e.g., precautions, warning, preclinical data), assuming that safety and efficacy issues can be resolved in the Company B's labeling.

- Framework for Cross-Labeling of Products "Not Individually Specified": A "not individually specified" product, as defined by AdvaMed, is a regulated product (i.e., drug, device, or biological product) intended to be used with, or delivered by, another separately packaged, regulated product, that is not named in the other product's labeling by its branded or proprietary name (e.g., generic, USP monograph, DESI, grandfathered drugs). Optimal labeling (and related jurisdictional) flexibility should be permitted for these products, because:
  - (1) adequate instructions for use can be conveyed in device labeling alone;
  - (2) concerns regarding the regulatory adequacy of the drug labeling can be addressed in clarifying guidance;
  - (3) exclusivity and misappropriation of data will not be an issue;
  - (4) commercial/product liability concerns of the drug manufacturers will be substantially reduced (because no individually specified drug will be named);
  - (5) postmarket change management will be less of an issue, because the types of drugs that fall within the "not individually specified" category (e.g., generic, USP monograph, grandfathered, DESI drugs) are restricted with respect to what changes can be made. It is understood, however, that even with generic and related products, minor changes to manufacture, formulation, and other aspects of the drug, could affect the combined system, and that the device company

may not be notified of these changes. AdvaMed therefore proposes that the device company be responsible for implementation of an appropriate risk management plan, including a risk assessment at the premarket stage, that would address such issues as: (a) the likelihood of post-approval changes to the drug; (b) the critical attributes that could affect safety and effectiveness of the combined system; (c) the impact, if any, that these changes might have on the combined system; and (d) the steps that the device company will take to attempt to detect and address all changes that could affect the safety or effectiveness of the combined system; and

(6) a wide array of postmarket mechanisms are available to ensure adequate oversight authority at point of commercialization.

- Framework for Cross-Labeling of Products “Individually Specified”: When a drug is identified by a branded or proprietary name in labeling, AdvaMed believes that commercial contractual arrangements are necessary to define the roles and responsibilities of the two parties, and to protect Company A’s proprietary information, exclusivity, and other commercial/product liability interests.
- Draft Guidance: AdvaMed recommends that cross-labeling clarifications be accomplished through a concept paper or advance draft guidance in the first instance, followed by draft and final guidances that proceed through notice-and-comment processes. AdvaMed members believe that this approach best accommodates the solutions desired by both FDA and sponsor companies, because combination law is not static and guidance allows for continued innovations and refinements over time.

AdvaMed commends the FDA for its ongoing efforts to focus on, and clarify, cross-labeling policies for combination technologies. We appreciate the opportunity to provide these written comments and proposals. Given the complexity of the issues presented by the FDA and the extensive responses AdvaMed has provided, we request the opportunity to meet with the FDA to further explain our views and proposals.

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### Introduction

The Office of Combination Products has identified draft cross-labeling guidance as one of its priorities for this year, and, as part of this priority, co-sponsored with the Drug Information Association, a Cross-Labeling Workshop held on May 10, 2005. AdvaMed commends FDA's co-sponsorship of this forum, and its development of an innovative framework of questions that has allowed interested stakeholders to begin to find solutions for cross-labeling concerns. AdvaMed members believe that cross-labeling is a defining area of combination law, that has the potential to sustain technological innovation or redirect its course. Accordingly, in addition to oral comments made on behalf of its members at the recent Cross-Labeling Workshop, AdvaMed has prepared these written comments, which build on its earlier oral remarks and further describe the consensus views of its members on cross-labeling policies.

In its Federal Register notice, the Agency provided a hypothetical non-cooperative research and development scenario in which potential cross-labeling issues are presented. (The Federal Register's hypothetical is described at Attachment 1 for convenience of reference.) The Agency then identified a number of public health and legal questions pertinent to that scenario, and requested responses and proposed resolutions to the concerns presented.

The hypothetical scenario offered by FDA addresses only separately packaged, regulated products that are used together (where one of the products is approved or cleared), and does not address combinations that are single entity products, two or more co-packaged products, or two or more separately packaged investigational products. At this time, AdvaMed's comments are limited to the specific scenario presented in the Federal Register (*i.e.*, separately packaged, regulated technologies). Labeling recommendations for other types of combination technology will be the subject of a subsequent submission.

For purposes of responding as directly as possible to FDA's specific scenario/framework, AdvaMed refers wherever appropriate to the device innovator entity as "Company B," and to the manufacturer of the approved drug<sup>2</sup> as "Company A." Additionally, although the FDA identified public health issues first in order in its Federal Register notice, AdvaMed's comments lead first with responses to the legal issues raised, because these legal issues provide an important foundation for all other comments we provide.

AdvaMed's comments to the hypothetical and related questions, are presented in four fundamental parts: (1) an overview of the principles that, in AdvaMed's view, should guide the development of cross-labeling policies; (2) responses to the legal questions and considerations, identified in the Federal Register; (3) responses to the specific public health issues, also identified in that document; and, (4) as Attachment 2 to these comments, proposed definitions of terms that are essential to clarifying cross-labeling concepts. Because AdvaMed members believe that its proposed definitions establish an important conceptual framework for many of its comments, it is recommended that Attachment 2 be reviewed as a first step to facilitate full understanding of this submission.

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<sup>2</sup> Throughout these comments, AdvaMed intends that its use of the term "drug" refer to both drug and biological products. Likewise, reference to the FDA's Center for Drug Evaluation and Research ("CDER") should be interpreted also to mean the Center for Biologics Evaluation and Research ("CBER"). Finally, while FDA's scenario focuses on labeling issues facing a device company when there is a non-cooperating drug entity, the scenario also should be interpreted as encompassing a drug company having to address labeling issues when there is a non-cooperating device entity.