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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.¹ 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

¹ 70 Fed. Reg. 15633 (Mar. 28, 2005).

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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 drug² 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.

² 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.

I. Overarching Principles for Proposed Solutions to Cross-Labeling Issues

As an important preliminary step to considering the specific cross-labeling issues raised by FDA, AdvaMed sought first to identify several overarching principles that should guide cross-labeling solutions. Four principles emerged from this preliminary discussion:

- (1) the principle of optimal flexibility, so as to encourage Company B's innovation and advancement of public health;
- (2) the principle of fairness, and the need to balance encouragement of innovation on the one hand, with equity on the other (*i.e.*, protecting Company A from undue responsibility and liability, and preserving that entity's proprietary information, consistent with existing law);
- (3) the principle that no new regulatory paradigm is needed, because existing statutory authority allows for a balance between flexibility and fairness, and clarifications can be made within this framework;
- (4) the principle of sound science and adequate oversight -- where all premarket issues of safety and efficacy would be addressed, in accordance with risk-based themes and regulatory standards, and adequate postmarket authority would be available to assist the Agency in its postmarket management of the product, once commercialized.

Details of each of these principles and, in particular, the statutory authority which accommodates these principles, follow.

A. Optimal Flexibility is Needed to Encourage Innovation and Advancement of Public Health

In its March 28, 2005 Federal Register document, FDA expresses concern that "valuable products may not be developed, manufactured, or distributed," if solutions are not identified with respect to cross-labeling policies.³ Congress too identified these concerns when it enacted the Safe Medical Devices Act of 1990.⁴ In creating the first statutory provision that recognized "combination" technologies and products, Congress cautioned that process impediments for combination technologies "may create barriers to the introduction of new, worthwhile devices onto the marketplace."⁵ In response to this concern, it urged the Agency, "in its administrative discretion," to reduce those burdens by creating streamlined solutions.⁶ Over the past decade, consistent with congressional sentiments, FDA has developed Intercenter Agreements and issued regulations that have allowed for optimal flexibility and

³ 70 Fed. Reg. 15633, 15633 (Mar. 28, 2005).

⁴ Safe Medical Devices Act of 1990, Pub. L. No. 101-629, 104 Stat. 451.

⁵ S. Rep. No. 101-513 (1990).

⁶ *Id.*

fostered innovation -- all in the interest of public health. We request that this important standard of flexibility continue to set the framework for cross-labeling solutions.

AdvaMed's responses to legal questions 3, 4, and 6, and public health questions 1, 2 and 4, highlight how optimal flexibility should be protected, preserved, and expanded.

B. Fairness

A corollary principle to permitting optimal flexibility to advance innovation and public health, is that this flexibility must be balanced against the legal rights and equities of any non-cooperating drug entity. Fairness requires that any cross-labeling solution not create needless exposure or burden for Company A, if Company A chooses not to pursue a pathway offered by Company B. Company A should not be required to assume potential risks, liabilities and burdens that it otherwise has decided not to accept.

AdvaMed's responses to legal questions 1 through 4, and public health questions 3 and 5, identify important fairness themes that should be factored into the Agency's cross-labeling proposals.

C. Existing Statutory Authority Allows Cross-Labeling Solutions to FDA's Hypothetical

There was significant discussion in the March 28 Federal Register and during the May 10 DIA/FDA Cross-Labeling Workshop concerning the legal authority needed to advance cross-labeling solutions that protect the interest of FDA, Company A, Company B, and the public health. As AdvaMed conveyed during the course of the Workshop, existing statutory authority already provides the framework for these solutions. Although clarifications will be needed in the form of a concept document, and draft and final guidances, the fundamental legal structure is now in place. More specifically: (1) Congress very clearly 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 separate and distinct category of regulated products, that would avoid barriers to innovation; and (3) the authority to develop flexible and unique solutions was granted not just for "combination products," as those products are currently defined, but more expansively to "combination technologies" generally. Details supporting these conclusions are provided below.

1. Congress established a fourth category of FDA-regulated products when it enacted combination authority.

The Federal Food, Drug, and Cosmetic Act ("FFDCA") and its legislative history clearly establish Congress' intent to establish combination products as a fourth regulated category, that is separate from drug, devices, and biological products. Combination products were first recognized as a distinct category of regulated products in the Safe Medical Devices Act of 1990 ("SMDA"),⁷ which referred very broadly to "[any] products that constitute a combination

⁷ Section 503(g) of the FFDCA, 21 U.S.C. § 353(g).

of a drug, device, or biological product.”⁸ The FDA noted that combination technologies were recognized “as distinct entities subject to regulation under the Act ... to alleviate the difficulty the agency had experienced in regulating such products.”⁹ The legislative history of the SMDA further indicates that Congress revised the definitions of drug and device, specifically “to accommodate the principle of [combination technologies].”¹⁰

A number of years later, in the Food and Drug Administration Modernization Act of 1997 (“FDAMA”), Congress reemphasized -- in even clearer language -- that combination technologies are a fourth category of regulated products. Specifically, FDAMA added a new classification provision, permitting a person to “submit a request ... respecting the classification of the product as a drug, biological product, device, or a combination product.”¹¹ This statutory provision thus explicitly added combinations as a fourth category of product, and the legislative history evidences that this fourth and distinct category was purposeful. In particular, S. 830 -- the Senate bill that resulted in Section 563 -- evolved from listing three categories of FDA-regulated products (i.e., drugs, devices, biologics, into which combinations were subsumed), to very directly separating out combination technologies as a fourth category of FDA-regulated products.¹²

2. Congress granted FDA authority to create unique solutions for this fourth category of products, that would avoid barriers to innovation.

As a fourth and distinct category of products, Congress granted FDA discretion and review authority to create unique solutions that would avoid barriers to innovation for this class. As one example, Section 503(g) of the FFDCA states that “[n]othing in [section 503(g)] shall prevent the [FDA] from using any agency resources . . . necessary to ensure adequate review of the safety, effectiveness, or substantial equivalence of an article.”¹³ The legislative history of this provision clarifies that FDA “will retain the authority to use any resources necessary to ensure an adequate premarket review.”¹⁴ Notably, Congress referred expressly to “authority” in describing the necessary “resources” that could be brought to bear. Congress thus clarified that the flexibility granted to FDA is not intended to be limited to administrative or personnel matters, but also applies to the legal authorities that may be applied to this category of product.

Perhaps the strongest evidence of Congress’ intent to prevent barriers to innovation for this fourth category of products, and permit innovative, unique solutions, is the hypothetical included in the Senate Report to Section 503(g). The hypothetical is almost precisely the same scenario as that raised by FDA in the March 28 Federal Register notice -- a device manufacturer with a novel device to deliver a drug, where the drug approval is held by an

⁸ 21 U.S.C. § 353(g)(1).

⁹ 61 Fed. Reg. 44396, 44400 (Aug. 28, 1996).

¹⁰ S. Rep. No. 101-513, at 30 (1990).

¹¹ Section 563 of the FFDCA, 21 U.S.C. § 360bbb-2 (emphasis added).

¹² S. 830 as introduced (“respecting the classification of an article (including an article that is a combination product ...) as a drug, biological product, or device”) to S. 830 as passed by the Senate (“respecting the classification of an article as a drug, biological product, device, or a combination product”).

¹³ 21 U.S.C. § 503(g).

¹⁴ S. Rep. No. 101-513 (1990) (emphasis added).

entity other than the device sponsor. In this Senate Report language, it is clear that Congress intended that Section 503(g) provide flexibility to this specific situation, by stating:

“The Committee believes that the provisions of this section also address the situation in which manufacturers of novel drug delivery systems may be required to obtain drug and device approvals, notwithstanding an approved application for the drug intended for use with the device. To the extent that the drug approval belongs to a person other than the device sponsor, a difficult route to the marketplace may result if the holder of the approved new drug application refuses to permit the device applicant reference rights to the safety and effectiveness data in the approved drug application. Where this occurs the device manufacturer currently is required to pass two distinct regulatory clearance barriers. Section 20 will eliminate the need to receive clearances from both the device and drug review divisions, and will vest authority in one agency group to conduct a premarket review.¹⁵

Importantly, Congress went on to state that it is concerned that, in some cases, safety and effectiveness “data from the approved new drug application is not available to the data sponsor . . . and may create barriers to the introduction of new, worthwhile devices onto the marketplace . . .”¹⁶ Accordingly, the Senate Committee requested that FDA “within its administrative discretion, streamline [the process] to reduce the burdens . . ., where a drug delivery system is not critical to the drug[’]s safe and effective use.”¹⁷

A further example of Congress’ intent to facilitate unique solutions for this fourth product category is provided in the Medical Device User Fee and Modernization Act of 2002 (“MDUFMA”). In MDUFMA, Congress extended the theme of flexibility in premarket regulation of combination technologies, by permitting FDA discretion to exercise flexibility in its postmarket regulation as well.¹⁸ The MDUFMA authority required only consistent and appropriate postmarket regulation of like combination products; it otherwise acknowledged that FDA’s postmarket regulatory authority should not be limited in crafting solutions for this category of products.¹⁹ With that additional provision of law, the entire regulatory spectrum for combination technologies is now permitted flexible use of FDA authority.

Finally, FDA’s past interpretation of 21 C.F.R. Part 3 also supports this theme of flexible use of authorities to regulate combinations. In particular, the FDA historically has stated that “it has the discretion to choose whether it will regulate [combination] products under the [A]ct’s

¹⁵ S. Rep. No. 101-513 (1990) (purpose and summary of Section 20) (emphasis added).

¹⁶ *Id.* (emphasis added).

¹⁷ *Id.* (emphasis added).

¹⁸ Section 503(g) of the FFDCA, 21 U.S.C. § 353(g).

¹⁹ See H.R. Rep. No. 107-728 (2002) (“this section ensures that the postmarket regulation of combination products will be consistent and appropriate,” “[n]othing in this section is intended to limit current postmarket regulatory authorities.”).

drug authorities, device authorities, or both if appropriate” and that “[m]aking this determination requires FDA to consider how the public health goals of the [A]ct can best be accomplished.”²⁰

3. The flexibility and unique solutions intended for “combination products,” extend to “combination technologies” generally

As described below, the statutory and regulatory provisions addressing combinations are not limited to technologies meeting the strict definitional criteria for “combination products” set forth at 21 C.F.R. § 3.2. Rather, the statutory language and legislative history support that “combination products” represent merely a subset of a broader class of combinations covered by combination law. More specifically, the flexibility of authority offered by combination law, extends not simply to “combination products,” but to the broader category of “combination technologies,”²¹ even if those technologies ultimately are reviewed under device authorities.

In the legislative history of the SMDA, the Senate Report includes an analysis of the provision that became Section 503(g) -- the provision that authorizes classification of combination technologies. In a three-sentence section of this analysis, it is evident that, while Congress limited application of a primary mode of action decision-making process to the subset of products defined as “combination products,” the more general flexibility contemplated by Section 503(g) was intended to apply to any products comprised of two different regulated products, *i.e.*, “combination technologies. Specifically, it stated the following:

“Section 20 amends Section 503 ... and describes the general procedures for determining the appropriate component of the FDA to review premarket submissions for products that are comprised of any combination of drugs, devices or biologicals. If the [FDA] determines that the primary mode of action of the combination product is associated with drugs, devices, or biologicals, then the [FDA] shall assign to the organizational unit within FDA charged with the premarket review of the element associated with the products primary mode of action, the responsibility to review the premarket submission of the combination product. However, the [FDA] will retain the authority to use any resources necessary to ensure an adequate premarket review.”²²

Thus, in the first sentence, Congress explained that the statutory authority on combinations was intended to apply to “premarket submissions that are comprised of any combination of drugs, devices or biologicals.”²³ Premarket processes for combinations were not to be limited in their application to the subset defined strictly as “combination products.” The next sentence ties the issue of primary mode of action specifically to the subset of combinations defined as

²⁰ 61 Fed. Reg. 44396, 44403 (Aug. 28, 1996) (rule establishing restrictions on the sale and promotion of cigarettes and smokeless tobacco under combination product authorities).

²¹ See Attachment 2 for a proposed definition of “combination technology.”

²² S. Rep. No. 101-513 (1990) (section-by-section analysis of Section 20, the amendment to Section 503).

²³ *Id.* (emphasis added).

“combination products” (and FDA’s proposed “primary mode of action” rule follows this congressional instruction). The third sentence in the analysis then expands the scope of the provision again, relating the clarification back to the first sentence -- that is, to all products “comprised of any combination of drugs, devices, or biologicals.” It is this statement, as noted above, that conveys that “the [FDA] will retain the authority to use any resources necessary to ensure an adequate premarket review.”²⁴ Thus, administrative discretion extends to “combination technologies” generally, and not simply to the subset defined as combination products.

In summary, the FFDCAs and legislative history convey three legal conclusions with respect to cross-labeling authority: (1) that a fourth and distinct statutory category exists for combinations; (2) that this fourth category can and should be guided by its own legal authority which permits flexible solutions; and (3) that all combination technologies benefit from this flexible authority. These conclusions collectively establish that there is a legal framework already in place, to provide cross-labeling solutions for the issues raised by FDA. It is this legal framework that guides virtually all of AdvaMed’s responses to the legal and public health questions provided below at Sections III and IV.

D. Sound Science and Adequate Postmarket Oversight

Resolution of all safety and efficacy issues is a final, but quite important, principle guiding AdvaMed’s proposed framework for cross-labeling solutions. AdvaMed members unanimously support the Agency’s stipulation in the Federal Register that all relevant safety and efficacy concerns must be addressed adequately, consistent with risk-based principles. Cross-labeling solutions also must ensure that the full array of postmarket authorities are available to FDA to ensure postmarket control and oversight of these technologies.

AdvaMed’s responses to legal question 5 and public health question 2 highlight this fourth principle.

II. Legal Issues

A. Question 1: Why do manufacturers of the two products sometimes not cooperate in bringing the new product to market? Are there any steps FDA can take to increase the likelihood of cooperation between the two manufacturers?

1. Why Manufacturers Do Not Cooperate: Examples

As discussed by a number of speakers at the FDA-DIA Cross-Labeling Workshop, manufacturers of drug and device products do not cooperate with research and development projects of the type specified in the hypothetical, for a wide variety of reasons. These reasons relate primarily to legal/regulatory exposure, commercial concerns, or both. While examples

²⁴ Id. (emphasis added).

would be too numerous to identify, some of the primary reasons identified by our member companies, are summarized below in table form:

Legal/Regulatory Concerns	Commercial Concerns
Product liability	Protecting intellectual property/assets
FDA exposure (QSR, postmarket compliance, etc.)	Protecting/directing business strategies
Fraud and abuse	Competing R&D and/or partnership interests with respect to drug delivery system
Intellectual property	Competing R&D and/or partnership interests with respect to drug
New safety/use concerns that could adversely affect drug franchise	Cost/resources/expertise in dealing with new regulatory and science issues
Non-related commercial disputes (e.g., between Co. A and Co. B)	Customer relations concerns

These various legal and commercial motivations for not cooperating, provide important context for AdvaMed's recommendations on what the Agency should (or should not) do to attempt to increase cooperation, as described below.

2. FDA Involvement to Encourage Cooperation

It was generally agreed during the FDA/DIA Panel discussions, that the FFDCa provides FDA with no authority to require cooperation at the premarket stage,²⁵ and AdvaMed would not support new legislation to provide this expanded authority. In the device industry's view, absent Company B's concurrence, FDA intervention -- even to request cooperation -- is not desired. Because commercial relationships often are sensitive and potentially difficult in the context of the hypothetical, any independent third party intervention (including from FDA), potentially could further adversely affect those business relationships. Where Company B desires FDA intervention, however, we request that FDA intervene to facilitate cooperation between the parties.

3. Potential Incentives to Encourage Company A's Cooperation

With respect to whether incentives should be offered to encourage Company A's cooperation with Company B, it is important to consider the potential value of incentives in relation to the reasons (identified above) why Company A might choose not to cooperate. User fee

²⁵ See Association of Physicians and Surgeons, Inc. v. FDA, 226 F. Supp. 2d 204 (D.D.C. 2002) (FDA cannot require manufacturers to conduct pediatric studies for products not labeled for pediatric use).

reductions, for example, are not likely to change the course of a non-cooperating Company A that is concerned about protection of intellectual property. This type of potential legal/business concern outweighs the benefit of any user fee reduction. Further, as Agency officials acknowledged during the FDA-DIA Cross-Labeling Workshop, under the Prescription Drug User Fee Act, the FDA is required to collect a certain amount of revenues, and reducing fees for some companies simply means that the total amount would be distributed differently, *i.e.*, others would need to pay more fees. Altering other parts of the law to create new incentives (*e.g.*, with respect to exclusivity benefits), likewise could have untoward consequences. Consequently, these types of regulatory solutions are not warranted or desirable, given that they do not address, and therefore likely do not adequately mitigate, the various underlying concerns of non-cooperating Company A.

AdvaMed notes, however, that, while FDA does not have authority to require the cooperation of Company A and Company B at the premarket stage, the Agency does have authority to require more active involvement by Company A at the postmarket stage. The various postmarket authorities that trigger this more active involvement by Company A, are identified and discussed in detail in response to legal question 5 below.

B. Question 2: How can FDA ensure that its approval of Company B's product does not improperly rely upon Company A's proprietary information?

In the interest of responding fully to this inquiry, AdvaMed has recast the issues into three sequential questions: (a) what information, under existing law, can be relied upon to support Company B's approval/clearance; (b) what information, under existing law, cannot be relied upon to support Company B's product approval/clearance; and (c) does existing law adequately protect and balance the proprietary data rights and interests of Company A, the innovation interests of Company B, and the FDA -- or is more needed?

1. Information Protected From Company B's Access and Use under Existing Law

AdvaMed members believe that any cross-labeling solution must protect data to which Company B by law does not have a right to reference. It is AdvaMed's view that, although Company B's innovation interests are important, they cannot be at the expense of any data rights and privileges Company A might have under existing statutory authority. For those drugs that were approved by the FDA under Section 505 of the FDCA, the Act sets forth the circumstances under which safety and effectiveness data and information which has been submitted in a new drug approval application for a drug and which has not previously been disclosed to the public shall not be made available to the public. Specifically, such data would not be disclosed until:

“the effective date of the approval of the first application under subsection (j) [*i.e.*, an abbreviated new drug application (“ANDA”)] which refers to such drug or upon the date upon

which the approval of an application under subsection (j) which refers to such drug could be made effective, if such an application [i.e., an ANDA] had been submitted.”²⁶

AdvaMed believes that these existing restrictions are adequate and have not resulted in improper reliance on proprietary information in the context of combination premarket reviews.

Although AdvaMed acknowledges that there has been ongoing debate regarding the ability to rely on findings or data under Section 505(b)(2),²⁷ these matters should continue to be resolved under drug authorities. Emerging combination law should not be used as a vehicle to further interpret or alter aspects of our drug laws, which are separate and distinct from combination authority.

2. Information That May Be Relied on by Company B

Existing authorities and policies establish several principles concerning information that may be relied on to support Company B's approval/clearance in the hypothetical offered by FDA. First, it is clear that both drug and device laws permit use of information in the public domain to support approvals, augmented as needed by data developed by Company B.²⁸ More specifically, as this issue relates to the hypothetical, drug authorities permit public domain information to be used in support of significant changes to an approved drug (including changes in dosage, routes of administration, and indications for the drug) -- again, augmented as needed with data developed by Company B.²⁹

Combination policies likewise provide guidance concerning the use of, and reliance on, public domain information. In particular, the Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health states that “an additional showing of clinical effectiveness of the drug when delivered by the specific device will generally not be required.”³⁰ Thus, combination policies acknowledge that prior approvals may be relied on as findings to reduce safety and efficacy data demands for combined drug/device products.

These principles permitting Company B's appropriate reliance on public domain information, have stood the test of time, have fostered innovation, and should remain fully protected and preserved.

²⁶ Section 505(l) of the FDCA, 21 U.S.C. § 355(l). Such information also may be disclosed: “(1) if no work is being or will be undertaken to have the application approved, (2) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted, (3) if approval of the application under subsection (c) is withdrawn and all legal appeals have been exhausted, and (4) if the Secretary has determined that such drug is not a new drug.” *Id.*

²⁷ See FDA, Applications Covered by Section 505(b)(2) (Draft, Oct. 1999).

²⁸ See Section 505(b)(2) of the FDCA, 21 U.S.C. § 355(b)(2) (may be based upon studies “not conducted by or for the applicant and for which the applicant has not obtained a right of reference”); 21 C.F.R. §§ 314.54, §14.20(b)(8).

²⁹ 21 C.F.R. § 314.50(d)(5)(iv).

³⁰ Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 1991).

3. Conclusion

AdvaMed thus believes that existing laws and policies are adequate in this area. They have balanced well the protection of any data rights and privileges that Company A may have under existing law, with the innovation interests and rights to access public domain information that Company B might have. FDA's interests are well served by preserving this balance, since it is likely that any change to existing law or interpretations of law that would adversely affect vested rights to data protection, would raise new risks of Agency challenge.

C. Question 3: How might approval of Company B's product affect the legal adequacy of the labeling for Company A's product?

For the sake of completeness, AdvaMed members analyzed this question from several perspectives. First, it reviewed issues relating to the adequacy of Company A's product labeling from a regulatory perspective. It next considered these issues from a commercial/product liability perspective, which, in turn, required a further analysis of whether or not Company A's product was a branded, proprietary drug. AdvaMed's conclusions and related recommendations with respect to these analyses follow.

1. Adequacy of Labeling from a Regulatory Perspective

During the FDA/DIA Cross-Labeling Workshop, there was significant discussion as to whether regulatory exposure might be created with respect to Company A's labeling, once Company B begins to market with new labeled conditions of use relating to Company A's product. Legitimate questions that Company A could ask with respect to the regulatory adequacy of its labeling include: (1) whether awareness of Company B's labeling might impute to Company A an obligation to revise its labeling,³¹ and/or (2) whether this awareness of a new use could trigger notification requirements for Company A under NDA or BLA authorities.³²

As described in Section I of these comments, existing combination authorities accommodate flexible solutions.³³ AdvaMed thus believes that Company A's legitimate concerns with respect to the regulatory adequacy of its labeling, could be resolved in a variety of possible ways. As one example, by guidance, FDA could provide a series of clarifications that could protect Company A from needless regulatory exposure. The clarifications might include the following:

³¹ 21 C.F.R. § 201.128.

³² 21 C.F.R. § 314.70.

³³ As noted above at Section II.D.3, this flexibility extends not just to combination products, but to combination technologies generally, even if they eventually are regulated solely under device authorities pursuant to 21 C.F.R. § 3.2. See Section 503(g) of the FFDCA, 21 U.S.C. § 353(g). The legislative history clarifies that this provision is intended to define premarket procedures for products "comprised of any combination of drugs, devices or biologicals." S. Rep. No. 101-513 (1990).

- An explanation of combination law authority, and why it represents a unique regulatory category that can be defined separately and distinctly from drug and device authority (thus avoiding Company A's drug compliance questions);
- a stipulation that Company B be solely responsible for premarket review of labeling adequacy (including adequate directions for use); and
- relatedly, a stipulation that approval/clearance of Company B's labeling would not itself cause misbranding of Company A's product. (In offering this suggestion, however, AdvaMed acknowledges that, if Company A subsequently begins to promote the combined use of its drug with Company B's device, FDA still retains postmarket misbranding authority over Company A, to oversee those activities.)

With these and related types of clarifications -- which the Agency in its discretion has full authority to make -- any regulatory concerns that Company A might have with its labeling, should be resolved.

2. Adequacy of Labeling from a Commercial/Product Liability Perspective

By contrast to regulatory concerns, not all commercial/product liability concerns may be resolvable, depending upon the type of drug that Company A has. In particular, the commercial/product liability implications will differ depending upon whether the drug is "individually specified" in labeling. Although the term "individually specified" has not been defined in FDA's regulations or regulatory history, as you will note from Attachment 2, AdvaMed members propose that it be defined to mean a "branded/proprietary"³⁴ drug. As described below, commercial/product liability remains a concern for these "individually specified" drugs.

Where a specific branded/proprietary drug has been identified on Company B's labeling, Company A will have legitimate questions with respect to product liability exposure. Company A, for example, will wonder whether the foreseeable risks identified in Company B labeling might render Company A warnings inadequate.³⁵ Company A will also ask the question of whether any confusion or conflicts with respect to Company B's labeling, might dilute the adequacy of Company A warnings and instructions for use.³⁶ At a more practical level, Company A may be concerned that it will become a more likely target for product liability challenge than Company B, particularly if the size and resources of the two companies differ substantially in favor of Company A.

Given these questions, AdvaMed members concluded that it would be difficult for FDA to take any action that could meaningfully protect Company A's commercial/product liability interests. There might be FDA clarifications that could mitigate these concerns somewhat, but

³⁴ This term is defined at Attachment 2.

³⁵ See, e.g., Kelso v. Bayer Corp., 398 F.3d 640 (7th Cir. 2005); In re Meridia Products Liability Litigation, 328 F. Supp.2d 791 (N.D. Ohio 2004) (holding that an adequate warning must fully and completely disclose the potential adverse reactions of a product).

³⁶ See id. at 814 (discussing the potential for overpromotion to dilute or nullify written warnings).

most likely not substantially. For example, even if FDA were to stipulate that Company B is solely responsible for the adequacy of the combined labeling, this type of clarification will not prevent the initiation of lawsuits against Company A, particularly if Company A is seen as having more significant financial resources. Further, although device preemption protections are conceivable if the product has been reviewed under PMA device authority, preemption cannot be relied on as an assured additional protection for Company A's drug product for a variety of reasons, including its novel application to combination technology.³⁷

Consequently, in the spirit of fairness, and to avoid undue exposure, AdvaMed is proposing that, where cross-labeling involves an "individually specified" drug -- that is, a branded/proprietary product -- there would need to be commercial contractual arrangements defining the roles and responsibilities of the two parties. Further development and FDA review of the product would not proceed without these underlying contractual understandings.

By contrast, where the drug product is "not individually specified" (i.e., has not been identified by brand name and is not proprietary),³⁸ AdvaMed believes that Company A's commercial/product liability labeling exposure concerns should be significantly diminished. (Examples of products where the drug is not individually specified include: external infusion pumps for use with first generation chemotherapeutic, analgesic, or antibiotic drugs; continuous flush catheters labeled for use with embolic or diagnostic agents; flow meters for delivery of anesthesia gas; and devices involving use of OTC anesthetics.) Under this "separately packaged combination technology"³⁹ scenario, Company A's drug would not be cited specifically in the labeling, and it would be the user and not the labeling that would drive selection of source. Also, because multiple sources of drug generally would be available, it could be more clearly demonstrated that Company B and not Company A is responsible for the labeling adequacy of the combined product. This proposed scenario is not unlike labeling of contact lenses that also identify lens solutions not individually specified -- an example of separately packaged products intended for joint use, with which FDA has significant experience.

Given the significantly diminished commercial/liability concerns for this category of drugs, it is AdvaMed's view that regulatory clarifications of the type described in III.C.1. above, should provide both adequate regulatory and product liability protection for products that are "not individually specified." To further protect Company A from liability, all clinically relevant information concerning use of the device with the drug would be included in the device labeling, as described in response to public health question 5.

³⁷ See generally Section 521 of the FFDCa, 21 U.S.C. § 360k; 21 C.F.R. Part 808 (establishing preemption from state and local device requirements). See *Medtronic, Inc. v. Lohr*, 518 U.S. 470 (1996) (finding no preemption of state law tort suit where device was cleared under the 510(k) notification process); *Horn v. Thoratec Corp.*, 376 F.3d 163 (3d Cir. 2005) (holding that FDA premarket approval preempts common law tort claims pertaining specifically to those device conditions specifically reviewed and required by FDA). See also *Bates v. Dow Agrosciences LLC*, 125 S.Ct. 1788 (2005) (limiting preemption of state tort claims brought under the Federal Insecticide, Fungicide, and Rodenticide Act). Although the latter case did not involve FDA-regulated products or the FFDCa, commentators have suggested it could impact future preemption cases under the FFDCa.

³⁸ This term is defined at Attachment 2.

³⁹ This term is defined at Attachment 2.

D. Question 4: What effect, if any, should the exclusivity of Company A's product have on whether FDA approves Company B's product without mutually conforming labeling?

To address the exclusivity implications of cross-labeling, AdvaMed members reviewed the issue from several perspectives: (1) they first asked whether attempting cross-labeling solutions when Company A had exclusivity protection, would be possible under existing authorities; (2) they next reviewed the practical implications of challenges by Company A, if cross-labeling solutions were thrust upon it in this context; and, finally, (3) they balanced the answers to both of these questions to reach conclusions, as described below.

1. An Overview of the Legal Framework

As to the broad issue of whether exclusivity rights would be infringed by the hypothetical offered by FDA, AdvaMed examined the principal purpose of FDA's exclusivity law. As noted during the FDA/DIA Workshop, the principal purpose of this law is to protect against inappropriate generic drug competition and inappropriate use of proprietary data. Under the proposed solutions offered by AdvaMed, there should be no inappropriate use of proprietary data -- all existing rights and benefits would be protected. With respect to generic drug competition, likewise, this would not occur in the hypothetical offered. If Company A has remaining exclusivity, it would be Company A's drug that users would purchase in connection with the marketed A/B combination. As with most companies regulated by FDA, any patent issues between Company A and Company B would then be addressed through appropriate (non-FDA) legal recourse. Thus, at least theoretically, exclusivity concerns should not be presented by the Agency's hypothetical.

2. Assessing the Risk of Challenge

AdvaMed next considered the practical issue of legal challenge, if cross-labeling were thrust upon an unwilling Company A in this context. From this discussion, AdvaMed members concluded that the risk of challenges would be real and potentially significant. Company A, for example, could attempt to assert that the device review process was a circumvention of the appropriate new drug approval processes contemplated by our exclusivity law. Company A also might assert that the device premarket review process is an imperfect surrogate, because it offers no right to receive patent certifications. As a more general challenge, Company A could further assert that FDA's exclusivity laws are very defined, specific, and all-encompassing, and that FDA has no flexibility to move beyond that statutory framework.

3. AdvaMed's Conclusions Concerning Arrangements With Drug Products Having Exclusivity Protection

Given the risk of potential challenge by Company A in this context, AdvaMed believes that such challenges, if brought, would require significant FDA resources; impede predictable pathways to market; and potentially slow down premarket reviews. For all of these reasons,

AdvaMed proposes that, where exclusivity rights remain for Company A's product, a commercial contractual arrangement must exist between Company A and Company B, for the product to be developed under combination authorities.

Question 4 (cont'd): Should the existence of generic versions of Company A's product affect whether FDA approves Company B's product?

As with the product liability/commercial discussion provided above, AdvaMed views products not individually branded and proprietary (i.e., "not individually specified") as having significantly broader and more flexible labeling solutions. As defined at Attachment 2, this category of products would include, for example, generic drugs, other off-patent drugs without market exclusivity, United States Pharmacopoeia ("USP") monograph drugs, drugs grandfathered by FDA, Drug Efficacy Study Implementation ("DESI") drugs, over-the-counter ("OTC") drugs, and broad categories of drugs specified only by therapeutic use or type.

For these drugs, AdvaMed believes strongly that there should be optimal flexibility in crafting labeling solutions, for several reasons:

- First, these are the products that would most benefit from innovation. It is often combination technologies that take older and/or off-patent drugs and refine their conditions of use, effectiveness and safety profile -- to the benefit of public health.
- Secondly, the regulatory framework at 21 C.F.R. § 3.2(e)(3) has in fact, on a case-by-case basis, already accommodated this type of flexible arrangement. Where drugs are "not individually specified" in Company B labeling, and are separately marketed, FDA in the past has not required cross-labeling for this category of "separately packaged combination technology," and has permitted device review.⁴⁰
- Thirdly, postmarket change management for these products is considerably less of an issue, and, thus, Company B's product is considerably less likely to present postmarket drug modification concerns. Existing laws for these categories of drugs (e.g., USP monograph, grandfathered, DESI, OTC drugs) do not allow for significant changes in dosage, modes of administration, indications, or other uses. If Company A desired any such changes after Company B brought its technology to market, Company A would need to make such changes using an entirely different regulatory pathway and marketing route -- in essence creating a different new drug product not covered by the "separately packaged combination technology."⁴¹
- Finally, if flexibility were employed with drugs "not individually specified," we believe FDA would not face any meaningful risk of challenge of the type presented by drugs with exclusivity interests, described above. Similar labeling flexibility has been

⁴⁰ A recent example is FDA's review of Genetronics' electroporation technology, which is intended to administer the generic drug bleomycin. FDA permitted this product to proceed through device review, and allowed device labeling to include all the drug-related information. See Transcript, Drug Information Association and the Food and Drug Administration Cross-Labeling Workshop: Combination Products and Mutually Conforming Labeling (May 10, 2005) (comments of Paul M. Goldfarb, M.D., FACS).

⁴¹ AdvaMed understands, of course, that some postmarket change management would be needed for products "not individually specified," and provides proposals in this regard at question 5 below.

employed by FDA with products such as “not individually specified” solutions used with contact lenses, and oncologics, and these innovations have advanced unimpeded by legal challenge.

Thus, for all of these reasons, AdvaMed proposes that, for generic and related drugs “not individually specified,” labeling policies be pursued with maximum flexibility, in the interest of public health.

E. Question 5: Would any other regulatory tools, such as conditions of approval on Product B, be useful in ensuring the appropriate degree of FDA oversight of the products used together?

AdvaMed believes that the Agency currently has a wide range of authorities to address and solve postmarket issues that might be presented by the hypothetical.

First, with respect to “individually specified” branded/proprietary drugs that might be used in the hypothetical, as noted above, AdvaMed is proposing that Company A and Company B define roles and responsibilities via contractual arrangements. These arrangements, in the ordinary course of business, would address postmarket management obligations, notifications to FDA, and interaction between the parties. FDA could further delineate obligations, as appropriate, because there will be cooperation between the parties in this context. Consequently, AdvaMed believes postmarket oversight will not be an issue for this category of products.

For labeling involving non-branded/non-proprietary drug products (*i.e.*, products “not individually specified”), there remains a wide array of authorities that FDA has now, and could further clarify and refine, to ensure that Company B and FDA are fully aware of postmarket changes as appropriate. By way of example, these authorities include the following:

- As recognized by FDA, Company B will be subject to conditions of approval if its device is reviewed through PMA authorities; special controls could be applied if the device product is processed through 510(k) device review.⁴²
- Both Company A and Company B would be required to notify FDA of any postmarket specification/manufacture changes, as required by law.⁴³
- Under Quality System Regulation (“QSR”) requirements, Company B is obligated to handle postmarket changes under design control/risk assessment procedures. It is understood, however, that, even with generic and related products, minor changes to manufacture, formulation, and other aspects of the drug, could raise new compatibility issues with the combined system. AdvaMed therefore proposes that Company B be responsible for assembling a risk assessment at the premarket stage, that would address

⁴² Sections 515(d)(1)(B)(ii) and 513(a)(1)(B) of the FFDCA, 21 U.S.C. §§ 360e(d)(1)(B)(ii), 360c(a)(1)(B); 21 C.F.R. §§ 814.44(e), 814.82, 807.87(l).

⁴³ 21 C.F.R. §§ 314.70(b), 807.81(a)(3), 814.39.

such issues as: (1) the likelihood of post-approval changes to the drug; (2) the critical attributes that could affect safety and effectiveness of the combined system; (3) the impact, if any, that these changes might have on the combined system; and (4) the steps that Company B will take to attempt to detect and address all changes that could affect the safety or effectiveness of the combined system. This risk assessment will be part of an overall life cycle risk management plan.

- For both Company A and Company B, postmarket reporting mechanisms would trigger the reporting of adverse experiences where required.

As evidenced by these enumerated authorities and proposals, for drugs “not individually specified,” the Agency will have sufficient postmarket oversight authority over both Company A and Company B, to allow the “separately packaged combination technology” hypothetical to proceed under device review.

F. Question 6: Do the legal issues that arise in the absence of mutually conforming labeling exist independently of § 3.2(e)(3), or can some of these issues be addressed by revisions or clarifications to this part of the definition of a combination product?

As noted above, AdvaMed believes quite strongly that revisions and clarifications needed to refine cross-labeling solutions, may be accomplished without new statutory or regulatory authority. In AdvaMed’s view, clarifications could be accomplished through a concept document in the first instance (i.e., an “advance draft guidance” document), followed by draft and final guidances that proceed through notice-and-comment processes consistent with good guidance practices.⁴⁴

AdvaMed members have concluded that guidance best accommodates the solutions desired by both FDA and sponsor companies, because it allows for innovations and refinements over time. Combination law is not a static law and the cross-labeling issues that are the subject of this Federal Register, will be solved through administrative discretion, as contemplated by the Safe Medical Devices Act.⁴⁵

Guidance is also appropriate because there already exists, at 21 C.F.R. § 3.2(e)(3), an adequate regulatory framework to publish further guidance clarifications. That regulation can be interpreted as recognizing three concepts essential to the proposals offered by AdvaMed: (1) it sets a threshold for cross-labeling based on “individually specified” products; (2) it preserves the flexibility to regulate products “not individually specified” under device authority, with no cross-labeling needed; and (3) more generally, Section 3.2 and related statutory authority and Intercenter Agreement policies, recognize that two separately packaged products may be regulated pursuant to the flexible solutions offered by combination authorities, even if the “separately packaged combination technology” ultimately is reviewed as a device.

⁴⁴ 21 C.F.R. § 10.115.

⁴⁵ See Section 503(g) of the FDCA, 21 U.S.C. § 353(g). In establishing a process for designation and review of combination products, Congress requested that FDA “within its administrative discretion, streamline [the process] to reduce the burdens. . . .” S. Rep. No. 101-513 (1990).

G. Question 7: Other legal issues; how can they be resolved?

With respect to other legal considerations that FDA should consider, as it begins to advance its cross-labeling proposals, AdvaMed offers the following recommendations:

1. The roles and relationships between Company A and Company B postmarket on such issues as promotion, recalls, and other compliance activities relating to labeling should be specified in guidance. Under the AdvaMed proposal, scenario one (involving branded/proprietary drugs) would have roles and responsibilities defined via contractual agreement. Under scenario two (where the drug is “not individually specified”), AdvaMed members agree that Company B should be the principal point of contact for all matters involving postmarket compliance.
2. Inevitably, after FDA and Company B reach resolution on the regulatory pathway, labeling and postmarket authorities for Company B’s device, similar scenarios (*i.e.*, a similar device manufacturer seeking to market its device for use with the same or similar drug as Company A’s drug), will repeat itself. We propose that like products be treated consistently,⁴⁶ in accordance with MDUFMA and administrative law principles.⁴⁷

III. Public Health Issues

As noted above, AdvaMed believes that its responses to the legal issues identified by the FDA, along with its proposed definitions of terms at Attachment 2, provide a framework for consideration and resolution of most cross-labeling issues, including the public health issues raised in the FDA’s Federal Register notice. Accordingly, in its responses to FDA’s public health issues discussed below, AdvaMed refers the Agency, in some cases, to its responses to the legal issues and to Attachment 2.

A. Question 1: What are the product development implications of mutually conforming labeling? Are products not developed because of a perception that mutually conforming labeling will be, or might be, required?

As noted in the introduction to these comments, AdvaMed has proposed definitions of terms to clarify, and serve as a conceptual framework for, cross-labeling solutions (*see* Attachment 2). In its response to this and the other legal and public health questions presented, AdvaMed relies on the term “cross-labeling.” While use of “mutually conforming” terminology is

⁴⁶ The Medical Device User Fee and Modernization Act requires that FDA “ensure the consistency and appropriateness of like products subject to the same statutory requirements.” Medical Device User Fee and Modernization Act, Pub. L. No. 107-250, § 204 (2002).

⁴⁷ *Airmark Corp. v. FAA*, 758 F.2d 685 (D.C. Cir. 1985), quoting *United States v. Diapulse Corp.*, 748 F.2d 56, 62 (2d Cir. 1984) (although courts generally grant “[d]eference to agency authority ... [and] expertise, such deference is not a license to ... treat like cases differently”); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997) (“What the FDA is not free to do, however, is to treat them dissimilarly and to permit two sets of similar products to run down two separate tracks, one more treacherous than the other, for no apparent reason”).

memorialized in the Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health, and historically has been applied to products we now deem as “separately packaged combination technology” products, the use of these descriptors is not widely understood by industry.⁴⁸ For this reason, AdvaMed has proposed not to use or define the term “mutually conforming.”

As we noted during the FDA/DIA Cross Labeling Workshop, it is very difficult to identify a lost opportunity that can be attributed solely to the requirement for cross-labeling, because cross-labeling issues are likely one of many factors that cause a company not to develop a novel product. Nevertheless, for the reasons given below, AdvaMed members believe that cross-labeling and related issues have a significant impact on the development of novel products -- particularly for small companies established and financed with a medical device regulatory pathway in mind.

The hypothetical presented by the FDA in its March 28 Federal Register helps to illustrate the various complicating factors that can inhibit product development. For example, a device company (Company B) seeking to develop a novel delivery system without the cooperation of the manufacturer of the drug to be delivered (Company A), may be required: to conduct large clinical studies; to conduct more than one pivotal clinical study; to conduct additional burdensome, preclinical testing; to develop detailed labeling for the drug as used with its device; to submit a new drug approval application for the delivery system; and/or to pay related drug user fees.

Given the nature of the device industry and the device market, these additional legal and regulatory responsibilities often lead device manufacturers to reach the business decision not to pursue development of innovative combination technologies. The device industry is made up of a large number of small, but innovative, companies that may not have the resources to proceed with development of a combination technology, without the cooperation of the approved drug product sponsor. Funding from the device investor community often is limited, and the potential profits to the device manufacturer may not support the investment, given the shorter life cycle of a device versus a drug, and the smaller device market. The regulatory burdens and related costs associated with cross-labeling, therefore, can be a significant impediment to a device manufacturer's development of combination innovations. Congress has acknowledged this concern and its potential impact on innovation, and has encouraged FDA to craft solutions where labeling issues do not serve as a barrier to the advancement of combination technology.⁴⁹

B. Question 2: How important is it that drug and device labeling be consistent with respect to intended use, dose, dosage form, strength and route of administration for the safe and effective use of the drug and device together?

Question 3: Should the decision whether mutually conforming labeling is needed for the safe and effective use of the products together be made on a

⁴⁸ Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 1991), at Section VII.A.(1)a.

⁴⁹ S. Rep. No. 101-513 (1990).

case by case basis? If so, what factors should FDA consider in determining whether mutually conforming labeling is necessary?

Question 4: To what degree should labeling conform? Does the labeling of the two products need to be identical? Consistent? Not contradictory? Is conformity more important for some parts of the labeling than others?

AdvaMed has provided a combined response to these three questions, because they all address consistency/conformity of labeling in the context of cross-labeling determinations. The decision as to whether cross-labeling is required, and related issues of drug and device labeling consistency, are defined by the following five essential elements and approaches:

- (1) Threshold Criteria for Cross-Labeling. As noted above, AdvaMed believes that the appropriate term, in the context of questions 2 through 4, is “cross-labeling,” rather than mutually conforming labeling. The definition of the term “cross-labeling” is particularly important, because it provides the primary analysis for decisionmaking in this area. “Cross-labeling,” as defined by AdvaMed at Attachment 2, is triggered when: (1) a proposed product (*i.e.*, device, drug, biological product) intended for use with a separately marketed, approved or cleared product, “individually specifies” the other product in its labeling; and (2) upon approval or clearance of the proposed product, its labeling will not be “generally consistent” with the approved or cleared product’s labeling. When cross-labeling is triggered, both Company A and Company B must modify labeling (*i.e.*, Company A will need to take steps to include information about the device in its product labeling, while Company B will need to address the drug to be used with its device in its labeling). The separately packaged products will be considered a “combination product,” subject to primary mode of action analysis to determine premarket review.

Conversely, cross-labeling will not be needed, when an approved or cleared 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; primary mode of action analysis will not apply.

- (2) Flexibility of labeling parameters. Labeling will be deemed generally consistent and, thus, will not trigger cross-labeling, if there is general consistency in the following three parameters of drug labeling: (i) indications; (ii) general mode of delivery; and (iii) drug dosage/dosing schedule. The term “generally consistent” is intended to mean “similar” and not “identical” with respect to these parameters. These principles of “general consistency” have been, and should continue to be, applied with optimal flexibility. For example, in recognition that, as technology evolves, drug conditions of use may inevitably be refined, the Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 1991) (“ICA”) permits all three parameters to be examined for the

“significance” of their change.⁵⁰ Instances in the past where FDA has applied this flexibility include: the Agency’s clearance of elastomeric infusion pumps for the continuous infusion of local anesthetics in either the hospital or home environment, where drug labeling did not specifically address home use; and clearance of continuous delivery systems for delivery of insulin where insulin was labeled for bolus administration via syringe (i.e., continuous versus single bolus doses).

- (3) Resolution of inconsistencies through risk analysis. Even if there are inconsistencies in the three essential drug parameters described in the ICA guidance, 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 there are no issues with regard to safety and effectiveness, and/or the risks could be adequately mitigated by Company B’s risk management plan, the differences should be permitted to be addressed in device labeling alone.
 - (4) Labeling consistency does not require conformance of all secondary aspects of drug labeling. The regulation at 21 C.F.R. § 3.2 and the ICA do not purport to address any secondary aspects of the drug labeling (e.g., warnings, precautions, preclinical data, etc.), beyond the three stated parameters of indications, mode of administration, and dosage. For this reason, flexibility historically has been afforded cross-labeling interpretations involving these other aspects of drug labeling.
 - (5) Full resolution of relevant safety and efficacy issues. The ICA affords CDRH flexibility to consult with CDER and resolve labeling differences in device labeling, and refers expressly to a CDER “consult” process to accomplish this objective.⁵¹ AdvaMed fully supports consultation from, or collaboration with, CDER as appropriate, to ensure relevant drug safety and efficacy issues are resolved.
- C. Question 5: Under what circumstances can adequate instructions for use be conveyed in one product’s label? For example, should FDA policy take into account the possibility that the labeling for a re-usable device might be lost over time?**

AdvaMed’s comments concerning adequacy of labeling from regulatory and commercial/product liability perspectives are provided at legal question 3. Its more substantive comments concerning labeling and adequate directions for use are provided above in response to public health questions 2, 3, and 4.

⁵⁰ Intercenter Agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health (Oct. 1991), at Section VII.A.(1)a.

⁵¹ Intercenter Agreement between the Center for Device Evaluation and Research and the Center for Devices and Radiological Health (Oct. 1991) at Section VII.A.1(a).

As to the content and format of labeling, AdvaMed believes that these issues should be determined by the designated lead Center, with consultation to other Centers, as appropriate. Because each combination's labeling will have unique characteristics, forthcoming guidance should not prescribe a general labeling content/format for this category of products. AdvaMed recommends that the device label include such supplemental drug information that is relevant to the safe and effective use of the combination technology.

On the issue of whether FDA policy should address the possibility that reusable device labeling might be lost over time, many devices -- including those that are not combinations -- are reusable. The question of a user's disposition of device labeling should not be part of any regulatory framework for labeling review. The obligations of manufacturers with respect to device labeling should focus first and foremost on the adequacy of the labeling itself.

- D. Question 6: How should FDA policy take into account the possibility that the product for which no supplemental marketing application was submitted (i.e., the approved product) might be reformulated or redesigned? Is it possible for Company B to sufficiently monitor product A to ensure that Company B is aware of formulation changes? Is it possible to identify in advance the characteristics of product A that should be monitored?**

AdvaMed addresses these issues in its response to legal question 5.

- E. Question 7: If mutually conforming labeling is not always required, what process should FDA follow in order to determine when it is required and when it is not required? When is the best time in the review process to make this determination?**

As expressed throughout these comments, AdvaMed and its members believe that the general criteria for determining when cross-labeling is required for separately packaged products used together, are already established in 21 C.F.R. § 3.2(e)(3). These criteria should be further refined through concept and guidance documents.

Cross-labeling determinations -- because they affect jurisdiction -- should be made at the same time that any determination is made regarding whether a product is a "combination product,"

for example, during initial review of a combination technology by CDER or CDRH or in the more formal Request for Designation ("RFD") process.

Timing is particularly important for small companies with limited resources. In these and related contexts, it is crucial that the sponsor understand the regulatory path and data requirements early in the process for efficient development of these products. It is undesirable and potentially financially disastrous for a small company, if additional significant data and regulatory requirements are imposed late in the product development, after much of the work has been completed.

F. Question 8: Other public health issues; how can they be resolved?

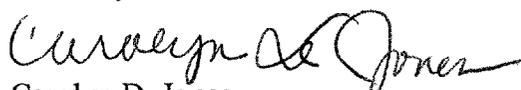
With the development of new, innovative combination technologies, there is a risk that new public health issues will arise. AdvaMed recommends that the Office of Combination Products ("OCP") continue to closely monitor the combination technologies that proceed through the FDA review processes, in order to identify public health or other issues as soon as they become apparent.

In AdvaMed's view, an active role by OCP is also crucial to ensure that application of Agency cross-labeling principles is consistent across all reviewing Divisions and does not unnecessarily hamper innovation by preventing or delaying approvals of novel devices. Specifically, AdvaMed continues to recommend that the OCP proactively monitor and manage the review process relating to cross-labeling throughout all stages of FDA's review. AdvaMed also recommends that the OCP actively participate and guide the framework for decision-making regarding when and to what extent consistency in labeling is needed, in order to bring its broader perspective to these discussions. Given its knowledge of historical cross-labeling policies and precedents across the Agency, the OCP is best positioned to facilitate resolution of cross-labeling controversies and concerns.

IV. Conclusion and Next Steps

AdvaMed again commends the FDA for its ongoing efforts to focus on, and clarify, cross-labeling policies for combination technologies and 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.

Sincerely,



Carolyn D. Jones
Associate Vice President
Technology & Regulatory Affairs

ATTACHMENT 1
FDA'S HYPOTHETICAL

Company A⁵² is currently marketing an approved drug product for intramuscular injection. Company B develops a device to deliver Company A's approved drug product for a different indication, to be delivered by a different method. No change in formulation to the drug product is needed.

Company B approached Company A to see if Company A would submit a supplemental new drug application to include the new indication and route of administration in the drug product labeling, but Company A refused. Company A also refused to provide a right of reference to data in its application.

Because Company B has been unable to obtain the cooperation of Company A, Company B approaches FDA and asks whether FDA would consider approving a device application stating that the device is intended to be used with drug product A delivered by the new route of administration for the new indication. Company B is willing to conduct all necessary studies to demonstrate that drug product A is safe and effective when delivered by the new route of administration by device B for the new indication.

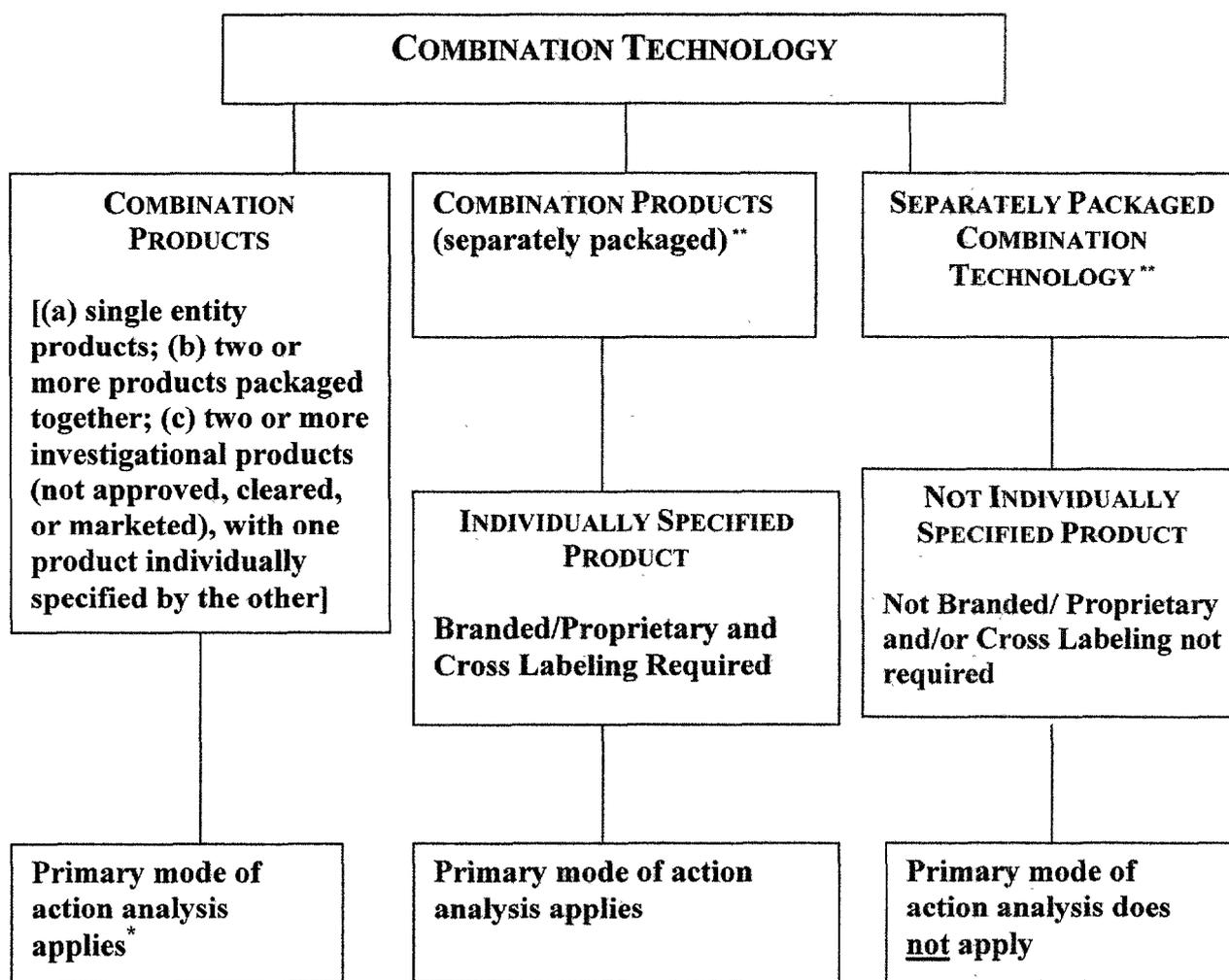
The end user would obtain the device from Company B and the drug product from Company A. The drug product labeling would make no mention of device B, the new indication, or that the drug product can be delivered by the new route of administration.

⁵² As stated by FDA in its Federal Register notice, for reasons of convenience, this hypothetical refers to Company A as a manufacturer of an already approved drug and Company B as the sponsor of a device to be used with drug product A, 70 Fed. Reg. at 15634, n.3.

ATTACHMENT 2

PROPOSED DEFINITIONS

Important terms used in this submission and recommended for adoption by FDA, are presented graphically below, followed by proposed definitions. All terms in quotations have been defined. This flow chart also identifies those labeling concepts that are covered by this submission, and those that will be the subject of a subsequent set of comments.



* Labeling for this category of products not addressed by this submission.

** These technologies include two or more separately packaged products, where one of the products is an approved or cleared drug, device, or biological product.

- “Combination Technology” -- A technology comprised of two or more regulated products (e.g., a drug and device, biological product and device, or biological product and drug), where the regulated products are intended for use together. As contemplated by statutory authority, “combination products,” as defined by 21 C.F.R. § 3.2, are a subset of this broader class of combinations.
- “Combination product” -- Those products defined at 21 C.F.R. § 3.2, as including:
 - (1) A product comprised of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic, that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
 - (2) Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
 - (3) A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
 - (4) Any investigational drug, device, or biological product packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect. 21 C.F.R. § 3.2.
- “Separately Packaged Combination Technology” -- A technology comprised of two or more separately packaged, regulated products (e.g., a drug and device, device and biological product, or biological and drug product), one of which is approved or cleared, which are to be used together, but that does not meet the regulatory definition of “combination product,” because: (1) labeling of one regulated product does not “individually specify” the other regulated product; and/or (2) there is general consistency of indications, mode of delivery, and drug dosage/dosing schedule.
- “Cross-labeling” -- This term, 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. This definition sets forth the threshold analysis under Section 3.2(e)(3), as to whether labeling of two or more separately packaged products to be used together, must be conforming. Cross-labeling will be

triggered when: (1) a proposed product (i.e., device, drug, or biological product) intended for use with a separately marketed, approved or cleared product, “individually specifies” the other product in its labeling; and (2) upon approval or clearance of the proposed product, its labeling will not be generally consistent with the marketed, approved or cleared product’s labeling, as further defined below.

When cross-labeling is triggered, both Company A and Company B must modify labeling (i.e., Company A will need to take steps to include information about the device in its labeling, while Company B will need to address the drug to be used with its device in its labeling). The separately packaged products will be considered a combination product, subject to primary mode of action analysis and related premarket review.

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 will need to address use of the drug and device together, and primary mode of action analysis will not apply.

- “Generally consistent labeling” -- Labeling of separately packaged products that generally conforms with respect to indications, mode of delivery, and drug dosage/dosing schedule. “Generally consistent” is intended to mean “similar” but not “identical” with respect to these parameters. Even if there are inconsistencies in these three parameters, labeling may nonetheless be considered generally consistent, if those inconsistencies can be addressed through a systematic risk analysis, as part of a risk management plan. Specifically, labeling will be “generally consistent,” if: (a) the results of a risk assessment indicate that there are no issues with regard to safety and effectiveness that cannot be addressed in Company B’s labeling; and/or (b) the risks can be adequately mitigated by Company B’s risk management plan. In such cases, the differences can be resolved in the proposed device labeling. Similarly, “generally consistent” labeling does not require consistency of secondary aspects of drug labeling (e.g., precautions, warnings, preclinical data), assuming that safety and efficacy issues can be resolved in the proposed device labeling.
- “Individually Specified” product -- 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 named in that other product’s labeling by its “branded/proprietary” name.
- “Not Individually Specified” product -- 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 a “branded/proprietary” name. Examples include: generic drugs, other off-patent drugs

without market exclusivity, USP monograph drugs, drugs grandfathered by FDA, DESI drugs, OTC drugs, and broad categories of drugs specified only by therapeutic use or type.

- “Branded/Proprietary Product” -- A product that has a branded/trade name, and patent and/or non-patent market protection, and that is not a generic, USP monograph, DESI or OTC drug, or a drug grandfathered by FDA.