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January 24, 2003

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

RE: Docket No. 02N-0445; FDA Regulation of Combination Products

Dear Madam or Sir:

Becton, Dickinson and Company (BD) appreciates the opportunity to submit these comments in response to the Food and Drug Administration's (FDA's) notice concerning the regulation of combination products [Federal Register, October 28, 2002].

Combination products as defined in 21 CFR Part 3, consist "of two or more regulated components, i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic" and also includes "two or more separate products package together in a single package or as a unit comprised of drug and device products..." BD manufactures various combination products, which consist of devices and drugs, either as single entity products, or as kits.

The innate complexity associated with products that do not fall into a pre-defined category is often ignored as legislation and regulations are promulgated. Thus, combination products often fall into two, or possibly three distinct jurisdictions within FDA. This increases the regulatory burden for both regulator and regulated, as well as creating an unclear process for companies to manage. We applaud the efforts FDA has undertaken to date, including the establishment of the Office of Combination Products, under the direction of Mark Kramer, the publication of standard operating procedures for the review of combination products and a commitment by the new office to update the Intercenter Agreements.

BD supports the positions that AdvaMed has taken both in its testimony before FDA's open public meeting in November 2002, and in its written comments to the docket. BD also has identified two additional areas where we believe improvements to current regulation of combination products can be made.

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I. Drug Re-importation

Current law[1] prohibits prescription drugs from being re-imported into the U.S. market. The goal of this legislation was to prevent adulterated and counterfeit products from being distributed to U.S. consumers. This law was enacted, however, without appropriate consideration of the potential impact on combination products. As FDA guidance indicates, if one company produces a prescription drug in the U.S., and that drug is purchased and shipped outside the U.S., it cannot be brought back into the country, other than by the original manufacturer of the drug. The result is that BD could not, for example, purchase a prescription drug manufactured by a second company in the U.S., ship that drug to one of BD's manufacturing facilities outside the U.S. for inclusion in a combination product, then re-import that combination product for sale in the U.S. This result would occur despite all the facilities being registered with and subject to inspection by FDA.

II. Labeling of Combination Products

Separate and inconsistent regulations currently exist for drugs, medical devices, biologics, and foods. For combination products, there is no single clear pathway to follow in determining how these products should be labeled. Moreover, different centers within FDA may apply the various requirements in different ways, which can result in excessive labeling information that causes confusion to the user or consumer, thus counteracting the basic purpose of labeling requirements. For small products, multiple labeling requirements and/or formats may be challenging or impossible to fit onto a single product. For example, combination products that consist of a device and an OTC drug are required to bear the labeling of both the included drug and device, even if the included drug is an alcohol swab. In addition, the drug labeling must follow the "Drug Facts" format, while the device labeling format is dissimilar. Further, much of the information is repeated, but is required to be stated by both the drug and device labeling regulations. BD has addressed this issue with FDA previously, in a December 7, 2001 letter to the Office of the Commissioner (copy attached.) To date, this issue has not been addressed.

In sum, BD believes that the current discount of the special needs associated with combination products is detrimental to the Medical Device industry as a whole, as well as

[1] Section 801(d)(1) of the Federal Food, Drug and Cosmetic Act

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to users and patients. We are optimistic that, through the Office of Combination Products, FDA will begin to address some of the specific issues associated with these products.

Thank you for the opportunity to comment on this important subject.

Sincerely,

Patricia B. Shrader, Esq.
Vice President
Corporate Regulatory Affairs and Compliance

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December 14, 2001

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Ms. Meg Hare
Office of the Commissioner
Food and Drug Administration
5600 Fisher's Lane, HF31
Rockville, Maryland 20857

Dear Meg:

This follows up our telephone conversation, in which we discussed labeling of combination products. As per your request, I am sending you several examples of combination product labels, along with some brief explanation. Please bear in mind that not all of these labels are currently used for products marketed in the U.S., as not all are in compliance with current FDA regulatory requirements.

A bit of background may be helpful in understanding why labeling, registration and listing, and good manufacturing practices are so significant for BD and similar companies. Like many medical device companies, BD makes a great variety of products, ranging from ACE® bandages, syringes/needles, catheters, procedural trays, and Vacutainer® tubes to sophisticated diagnostics including flow cytometers and reagents and rapid antimicrobial susceptibility test instruments and reagents. In addition to developing new and sometimes sophisticated devices, BD also manufactures and packages numbers of products that are designed to be simple and convenient for users. The majority of products that BD distributes are intended for professional use, although some are not prescription products. BD also distributes products that can be used by both professional and lay users; e.g. syringes.

With respect to combination products, those that BD currently produces fall into two general categories. First, BD packages devices and drugs together in a kit format; the drug may be either Rx or, more typically, OTC. Other BD products are "true" combinations; e.g. saline or heparin flush syringes and antibiotic impregnated catheters.

You will find attached numerous examples of BD's labeling for combination products. The first group is labels for kit combinations. Attachment 1 shows the current unit label for an IV Start Pak (IVSP), which is an I.V. site preparation kit. BD Dressing Change Kits and Procedural Kits also fall within this group of combination products. Typically, the kit components include one or

more medical devices and one to three drug products (Rx or OTC). Examples of these drug products are Benzoin Swabsticks, Iodophor Swabsticks, Povidone Iodine Preps and Alcohol Swabsticks. Of these products, BD manufactures only the Persist Povidone Iodine Swabsticks.

The label in Attachment 1 is representative of the look of the entire product IVSP family. As you can see, one of the issues BD faces with putting Drug Facts labeling on this kit label is the small size of the label. The attached label is close to actual size (approximately 5.25" x 3"). This same issue of size exists with other BD products, whether true combinations or kits; see, e.g. Attachments 2 and 7. The small size of the labeling makes it difficult for users to read. In addition, because these products are all intended for and used by healthcare professionals, the value of the information in this format and location may not be as great as for lay users. In this instance, a labeling exemption and/or alternative means of conveying the information may be appropriate.

A second issue that BD and other device companies face is control of drug companies' labeling. For example, BD may purchase Alcohol Swabs from Company "A", who puts their Drug Facts labeling on an outer box rather than on each individual packet. The box may contain 500 individual alcohol swab packets. If BD buys the box of 500 and puts one each into a kit, we must put the Drug Facts labeling on our product, either by labeling the immediate package or the outer box. If BD elects to change the actual package label, there is a risk of compromising the integrity of the product, through additional handling, whether we overlabel (which typically is prohibited for drugs, although not necessarily for devices) or repackage in a new outer package or box. Although we may ask the drug manufacturer to change its labeling to meet BD's regulatory requirements, they often are unwilling to do so, particularly if BD is not a significant purchaser of the product.

There are additional problems we have faced with respect to the labeling of combination products. For example, if we prepare new labels for a product that is sent to us already labeled or if we produce package labels that reflect the required labeling for the drug component in the package, a system must be in place to assure that if the drug manufacturer makes a change to labeling, BD will be notified in advance, in sufficient time to make the change to our label. This system must also be in place when BD elects to put all of the Drug Facts labeling information in a Product Insert, rather than directly on a product label. Another problem occurs when BD receives alcohol swabs (or similar drug product components) from different vendors; BD might have to change labels and/or package inserts each time we change suppliers, which can occur on a lot-to-lot basis.

The second kit label we have provided, shown in Attachment 2, is the label for a Bactec® blood culture procedural tray. This product must comply with in vitro diagnostic medical device requirements (21 CFR 809.10) and, because it contains an isopropyl alcohol pad, with Drug Facts labeling. As you can see, in order to meet the size requirements for Drug Facts, we have had to significantly compress the IVD labeling. In order to justify not including all required device information on the package, BD must rely on the small size exemption for IVD labels, although it is not clear that this exemption applies in such a situation. Again, from the standpoint of user friendliness, some of the label information is quite small and the lack of consistent format makes the label difficult for the user comprehend.

Next you will find examples of some single entity combination products, including Persist™ and Persist Plus™, which are sold both as kit components and individually, and flush syringes. Attachment 3 shows the draft Persist site prep label, in actual size. We have not yet been able to finalize the label, because we have used 5 point type in order to fit the required information; the regulation, as you know, requires a minimum of 6 point type.

Attachment 4 shows the current Persist Plus label, as copied from the actual package. Please note that Persist Plus is not available for sale in the US at this time. Attachment 5 shows the draft Drug Facts label for Persist Plus. As currently configured, it will fit on the current package size, but there is not sufficient space for the product name to appear.

Attachment 6 is the current box label, with directions for use, for a standard BD syringe (with needle); the portion of the label bearing the manufacturer's name, address, product name, etc., is not shown. The labeling is in compliance with medical device regulations at 21 CFR 801. When BD fills the syringe with saline or heparin and distributes it, rather than selling the syringe to a pharmacy or hospital and allowing an intermediary to fill it, the result is a combination product, the flush syringe. Attachment 7 is the actual label copy for the heparin flush syringe (3 ml), which has been designed primarily to meet medical device labeling requirements. Attachment 8 is the labeling included with the flush syringe (package insert), which contains the required information for a prescription drug.

To summarize the issues identified above, the current labeling requirements for combination products often do not serve the users of the products well and may be difficult for manufacturers to implement. Size and packaging waste considerations suggest that the minimum important information should be provided on the immediate product package, in a font size that is legible for most users. The information required by professional and lay users, as well as the language in which the information is conveyed, may be different.

A consistent format within the label would be easier for users to understand and follow. It also is important to take into consideration whether labeling provided by a particular means (immediate product label, package label, package insert) is likely to be seen by the user of the product. Finally, manufacturing considerations, including the need to change packaging (raising the potential for product compromise) should be taken into account. All the foregoing suggest that flexibility in the application of rules for labeling of products is important and should be built into any regulatory approach.

The possibilities for a new approach to the labeling of combination products include:

-A uniform format for combination product labels for appropriate groupings of products

-Expansion of the current labeling exemptions to accommodate combination products

-Labeling regulations or guidance that recognizes the differences between the information needs of professional and lay users and that takes into consideration the most effective means of conveying information to that group

-General guidance for the labeling of combination products

BD and other manufacturers would be happy to discuss these issues further with FDA and to work with the agency to identify approaches that will best serve the public's interest in labeling of regulated products. We very much appreciate your interest in this issue. If I can be of further assistance, please do not hesitate to call (201-847-7429).

Sincerely,

Patricia B. Shrader
Vice President
Corporate Regulatory

bcc: C. Finch
N. Isaac
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