



Combination Product Labeling¹

By Michael Gross, PhD, RAC

This article, the fourth in a series² on US Food and Drug Administration (FDA) regulation of combination products, considers the topic of combination product labeling. Section 201(m) of the *Federal Food, Drug, and Cosmetic Act* defines “label” as “...written, printed or graphic matter upon any article or any of its content or wrappers or accompanying such article...” In this article, “labeling” is distinguished from the label affixed to a drug product and/or its packaging, and refers mainly to directions for use (i.e., prescribing information and instructions for use (IFU)). Instructional, storage-related, or precautionary statements on the primary label may also be considered to be labeling. This article does not cover regulation of combination product advertising and promotional materials, which also fall within the definition of labeling.

Most of what FDA has publicly discussed on the subject of combination product labeling concerns the “cross-labeling issue.”³ The agency has said little about combination product labeling requirements in general beyond the fact that combination products are misbranded if directions for use are inadequate, and FDA may apply any regulatory resource it deems necessary to ensure a combination product’s safety and effectiveness.⁴

This article summarizes how combination products are labeled, how predicate labeling regulations may be applied and what has been said thus far by FDA on the labeling of combination products.

Current Regulatory Frameworks

To ensure safe and effective use, when drafting labeling manufacturers should consider predicate labeling regulations for each constituent part of a combination product. Predicate labeling regulations for drugs, biologics and medical devices describe format and content requirements for their labels and labeling. In the absence of regulations to the contrary, these requirements should also be applied to the constituent parts of combination products when they are separate (i.e., cross-labeled combination products), when they are co-packaged (kit combination products) and when they are physically combined (single-entity combination products).

Requirements for the content and format of labels and labeling for human prescription drugs and biological products are defined in 21 CFR 201. Counterpart regulations describing the content of a medical device label can be found in 21 CFR 801.1. Device label format requirements are described in 21 CFR 801.15. Finally, 21 CFR 801.5 defines the elements required for the directions for use for a medical device. To assure the safe and effective use of any combination product, its label and labeling must contain all the information necessary for its use. Thus, compliance with the label and labeling requirements for each constituent part should be reflected in the labels and labeling of all combination products regardless of their type.

The Inter-Center Agreement (ICA) between the Center for Drug Evaluation and Research (CDER) and the Center for Radiological Health (CDRH)⁵ suggests that kits that include one or more devices and drugs as separate entities in a single package and whose primary intended purpose is a device function (e.g., a surgical kit or tray) are combination products called convenience kits. Interim regulatory guidance on how to label these convenience kits was issued by CDRH in 1997.⁶ The guidance applies only to convenience kits whose components are either legally marketed preamendment devices, are exempt from premarket notification or have been found to be substantially equivalent through the premarket notification process. When they are cleared by FDA for marketing, these constituent parts must be labeled according to their premarket notification clearance. The labels for such convenience kits tend to be relatively simple, identifying the assembler or manufacturer of the kit and its intended use. Currently, FDA exercises enforcement discretion by not requiring additional premarketing clearance for convenience kits identified in the interim guidance, if they consist of components that are legally marketed and where the assembler/manufacturer reasonably concludes that any further processing of the kit and its components by the manufacturer or assembler did not significantly affect the components’ safety or effectiveness. When an approved drug (e.g., local anesthetic) is included in these “device” kits, a consultative review by CDER is likely. Often, the approved package insert for the drug is supplied as part of the kit.

The ICA between CDER and CDRH also addresses the labeling of certain drug delivery devices, many of which are combination products.⁷ It suggests that for an unfilled drug delivery device, when it is not possible to develop adequate drug labeling that makes it possible to substitute a generic marketed device for the device that was used during development for use with a marketed drug, and the characteristics of a device required for the safe and effective use with the drug can not be specified, then the device and drug are regulated as separate entities and their labeling should be “mutually conforming.” Uncertainties about the meaning of this term were discussed as part of a workshop held in 2005 to discuss the legal-regulatory issues concerning cooperation, or the lack thereof, between manufactures of different medical products types that are used together.⁸ This discussion included the differences between the terms “mutually conforming,” “individually specified,” and “cross-labeled,” and the meaning of “labeling of the approved product would need to be changed” when defining a combination product.⁸ Some clarification was achieved regarding circumstances when products used concomitantly, may or may not be combination products, and when cooperation between their manufacturers may or may not be necessary. For general-purpose devices (e.g., pumps, administration sets, catheters and nebulizers) the absence of mutually conforming labeling is not a problem as long as the devices can be used with different drugs and biologics and claims for use with a specific drug or biologic are not made.

Insight into FDA’s thinking on the labeling of single-entity device-drug combination products may be gleaned from a draft guidance on drug eluting coronary stents issued in March 2008 by CDRH and CDER.⁹ The draft proposal describes the information that the agency considers appropriate for inclusion in the labeling of drug eluting coronary stents. The content of the proposed labeling is a mixture of the device IFU and the drug or biologic package insert.

Discussion

While uncertainty exists over what constitutes “conforming labeling” and “cross-labeling,” in some respects, the combination product type described in 21 CFR 3.2(e)(3) represents the simplest labeling case because the labels and labeling of the constituent parts are separate. A deviceXdrug combination product, a deviceXbiologic combination product, a drugXdevice combination product and a biologicXdevice combination product will all utilize a separate IFU for the device and a separate package insert for the drug or biological product constituent parts. This is also true for drugXbiologic and biologicXdrug combination products but these cases exclusively involve separate package inserts. In all of these cases, the labeling

of one constituent part will refer to the counterpart constituent part and vice versa. What is unclear is the form this reference must take. For example, does the cross-reference need to be stated in terms of brand name, pharmacologic class, etc., and, is there a specific section in the IFU and the package insert where cross-labeling should occur?

In general, the labeling of kits¹⁰ is more straightforward. FDA has provided some guidance on convenience kits that, for the most part, does not involve additional labeling. How to label other device+drug or device+biologic kits is less clear. Unless otherwise instructed by a CDRH reviewing division, sponsors should affix an additional primary (overall) label to the kit and provide instructions for (kit) use. Based on precedent (e.g., a vial drug or biologic co-packaged with a syringe or measuring device), the primary label of drug+device combination products would not necessarily cite the device constituent; however, the package insert would, at a minimum, include a description of the device in the “How Supplied” section and instructions for using the device with the co-packaged drug or biological product in the “Dosage and Administration” section.

For a device constituent that has its own 510(k) clearance (e.g., syringe, vial adapter, needle safety device), note that FDA reviewers of drugs and biologics may require more-detailed package inserts and IFUs than normally supplied by the device manufacturer, although both should be consistent. Devices in kits for which primary regulatory jurisdiction lies with CDER or CBER, if cleared for general use, become “cleared” for the more specific use via more specific labeling.

Similar to cross-labeled combination products that involve a device constituent part, the prescribing information for drug+biologic or biologic+drug combination products should, at a minimum, specify the use of the counterpart constituent in the “How Supplied” and “Dosage and Administration” sections.

Single-entity combination products exhibit the most complex labeling. The labeling of drug-eluting coronary stents provides a model. The labeling of these device-drug and device-biologic combination products should typically conform to device requirements for the primary label affixed to their packaging, and their IFU should constitute a hybrid of device and drug (or biologic) labeling.

Single-entity drug-device or biologic-device combination products involve hybrid labeling reflecting the addition of a description of the device constituent in the How Supplied section and instructions for the use of the device with the drug or biologic in the Dosage and Administration section of the Prescribing Information or in the Medication Guide. The label and labeling of a drug-biologic or a biologic-drug single-entity combination product is

straightforward. Only a single package insert is needed and there is only one set of format and content requirements with which to comply.

Summary and Recommendations

Currently there is no FDA regulation or general guidance on how to structure labeling for combination products. Structuring labeling for cross-labeled combination products should be relatively straightforward; structuring kit labeling may be somewhat more complex; and the labeling of single-entity combination products can be very complex. How to structure a label for a combination product should be determined, in part, by considering existing rules on the format and content of labels and labeling of the individual constituent parts. When drafting labeling for a combination product, manufacturers should also consider precedents involving identical, similar or analogous products identified through regulatory intelligence. Labeling for a particular combination product will be a natural part of discussions between the sponsor of a combination product and the FDA center with primary jurisdiction as the submission of a marketing application nears.

References

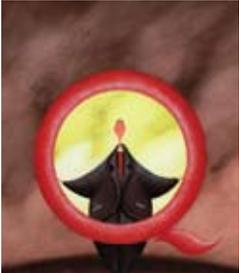
1. The symbols used in this article and in future articles in this series are as follows: X refers to a cross-labeled

- combination product, + refers to a kit and – refers to a single-entity combination product.
2. Terminology and conventions used throughout this article are defined in the first two articles in this series: The Combination Product Problem, *Regulatory Focus*, 14(6) 43-45, 2009 and, Combination Product Terminology, *Regulatory Focus*, 14(8) 44-46 (2009).
3. Gross M. "The Combination Product Problem." *Regulatory Focus*, 14 (6) 43-46 (2009).
4. 21 CFR 3.1.
5. Inter-center Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health, 1991.
6. "Convenience Kits Interim Regulatory Guidance," CDRH, 20 May 1997.
7. *Ibid* 5.
8. Transcript of an FDA/DIA Workshop: "Combination Products and Mutually Conforming Labeling" (10 May 2005).
9. Companion Document to the *Draft Guidance for Industry: Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies* (March 2008).
10. 21 CFR 3.2(e)(2)

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Author

Michael Gross, PhD, RAC, is a senior consultant with the Biologics Consulting Group specializing in quality, regulatory and technical issues for combination products. Over his 30-year career, he has worked for FDA and drug, biological product and medical device manufacturers. Gross has spent more than 20 years working on combination product problems. He can be reached at mgross@bcg-usa.com.



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10903 New Hampshire Ave., Bldg. 66 Room 3438
Silver Spring, Maryland 20993-0002
e-mail: collin.figueroa@fda.hhs.gov

