CPC COMBINATION PRODUCT COALITION

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VIA ELECTRONIC MAIL

Thinh X. Nguyen
U.S. Food and Drug Administration
Office of Combination Products
Building WO32; Room 5142
10903 New Hampshire Ave
Silver Spring, MD 20993

Re: Comments on Cross-Labeled Combination Products

Dear Thinh:

The Combination Products Coalition ("CPC") thanks you for meeting with us on March 2, 2011, to discuss the issues in combination product policy currently facing the Agency and industry. We enjoy working collaboratively with your office, and we have found these periodic meetings to be very helpful in guiding our group's work and thinking. During our meeting, we spent a good amount of time discussing cross-labeled combination products. Ultimately, our group took an action item to analyze the questions we debated during the meeting and to submit comments to the Office of Combination Products ("OCP") with our thoughts.

As you know, the CPC is a group of leading drug, biological product, and medical device manufacturers with substantial experience and interest in the combination products area. Our members are extraordinarily diverse, ranging in size from start-ups to multi-billion dollar manufacturers. Because of this diverse, cross-industry membership, we think the CPC brings a broad and unique perspective to issues affecting combination products.

We have organized our comments around the major questions that were posed and discussed during our March 2 meeting. Question 1 considers the overarching issue of whether a cross-labeling category is needed, and the remaining questions address related issues.

1. **Key question: Do we need a cross-labeling category? Does it have a special meaning or purpose?**

The cross-labeling category is useful in rare circumstances, when mutually conforming labeling that specifically cross-references another product by brand is necessary to ensure safety and effectiveness. For example, cross-labeling might be necessary when the particular use of the

two products has been demonstrated as safe and effective, while other uses or products have not. These other uses and products are not necessarily unsafe or ineffective, they are just not yet proven.

Indeed, cross-labeling triggers relatively few unique regulatory requirements. Appendix A describes where regulation as a cross-labeled combination product triggers unique requirements that help ensure the product's safety and effectiveness. That said, one important benefit of being regulated as a cross-labeled product is that it enables access to the OCP and its assistance with coordinating product review and discussion among the Centers. This type of oversight and coordination helps to ensure the product's ultimate safety and effectiveness.

However, in many circumstances, products used concomitantly will satisfy the need to ensure safety and effectiveness. Most products distributed separately but used together are concomitant use products, not cross-labeled products. As FDA has described, many products used together entail "the concomitant use of drugs, devices, and/or biological products that are not 'individually specified' in the product labeling (see 21 CFR 3.2(e)(3))."[1] Below are examples of concomitant use products:

- Erbitux (cetuximab) for use in combination with radiation therapy to treat patients with squamous cell cancer of the head and neck (SCCHN) that cannot be removed by surgery (unresectable SCCHN)
- Vectibix (panitumumab) and EGFR pharmDx(r) Test Kit
- DakoCytomation's c-Kit (9.7) pharmDx and Gleevec

These products do not reference each other by name and thus do not qualify as cross-labeled combination products. Nevertheless, FDA has determined that safety and effectiveness are ensured either by non-specific brand references or by a unilateral reference. Cross-labeling was not necessary.

2. What is cross-labeling and what is mutually conforming labeling?

To have a cross-labeled product under 21 CFR 3.2(e)(3), you must have *both* mutually conforming labeling that references the product *by brand*, as well as some level of *cooperation* between the parties.

Point 1: The mutually conforming labeling must be a cross-reference to a *specific brand*.

- Where FDA permits merely a cross-reference to a generic class of products, FDA apparently has concluded that the issues can be evaluated at a general level for the whole class of cross-referenced products, without cooperation from any particular manufacturer of the class of products.
- On the other hand, if the safety and effectiveness issues among the class of products vary from brand to brand, FDA should not permit a general cross-reference and should instead require a cross-reference to a specific brand. That, in turn, suggests that a cross-labeled product necessarily means the reference will be to a specific brand and

[1] FDA, *Other Types of Combinations of FDA Products,* available at: http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101464.htm (last accessed March 29, 2011).

that FDA needs cooperation between the two companies to assure the safety and effectiveness of the combined product.

Point 2: Further, the development, production and approval of a cross-labeled combination product requires *cooperation* – both initial and continuing – of the two parties because the only intended use of each of the two articles is to be used with the other.

- If mutually conforming labeling that specifically cross-references another product by brand is necessary to ensure safety and effectiveness, the products are a combination product and cooperation at least in labeling is required. It is hard to imagine how two articles that comprise a true combination product would be developed if the two companies were not cooperating together. If, on the other hand, mutually conforming labeling that specifically cross-references the products by brand is not necessary to ensure safety and effectiveness, the products are not combination products.
- Further, the mutually conforming labeling necessary to achieve combination product status can be sustained only if the companies continue to cooperate with each other.
- As written, the regulation focuses narrowing on the mutually conforming labeling issue and fails to address the broader, related issue of cooperation.

3. A cross-labeled product has to be a combination product initially because each product "needs" the other. But does the product need to stay that way? Can you "undo" the combination product status?

Yes, the companies cooperatively may decide to "undo" the combination product status by relabeling each of their products. Also, either of the companies may undo cross-labeling by relabeling its product without the other company's cooperation. For example, a manufacturer of a drug that cross-references a specific device may relabel the drug product to reference a general device type. Obviously any relabeling would need to comply with regulatory requirements.

The Agency or manufacturers also may foresee that cross-labeling is not needed at the outset. As discussed above, cross-labeling is needed only when necessary to ensure safety and effectiveness of the product(s). In this case, the Agency or manufacturers could decide upfront that cross-labeling is not warranted.

Subsequent approvals also may introduce products that can be used together, yet do not require relabeling and thus are not combination products. Thus deeming a product as "cross-labeled" can be problematic in the face of new approvals that would introduce concomitant uses. Take the example of an approval of a new device for delivering an already-approved drug. If: (1) a new device can be developed for administering the drug; (2) the device is slightly different but substantially equivalent in function to the existing device used for delivering the drug; and (3) the new device could be approved without requiring a change to the labeling for the drug, then the second device is not part of a combination product because its approval did not require the relabeling of the drug. However, if the drug labeling specifies the use of a specific delivery device and that delivery device is not used, this would constitute off-label use. If, on the other hand, the new device is different enough from the old device that its proper use would require new labeling for the drug, the new device would need to be part of a combination product, and the cooperation of the drug manufacturer would be required.

4. **Do you at some point *need* to undo the combination product status (e.g., new science/new products developed)? Stated another way, is the cross-labeling category overused in order to exclude products (e.g., label such that use of another product would be off-label)?**

FDA has the ability to decide what labeling must address for safety and effectiveness purposes. However, FDA does not have the ability to address labeling issues due to market or competition reasons. Absent reasons of safety and efficacy, just as FDA cannot order companies to cooperate to achieve mutually conforming labeling, FDA also cannot compel companies to relabel a product to require use with a broader class of products.

To illustrate our point, we'll use the example of an approval of a new device for delivering an already-approved drug. If relabeling is necessary to assure safety and effectiveness, we believe that FDA is without legal authority to approve the device in the absence of the willingness of the drug manufacturer to relabel its drug. FDA also is without legal authority to order the drug manufacturer to perform that relabeling. FDA simply has no legal grounds for telling a drug manufacturer that it must relabel its drug in order for the Agency to approve a device that would then take advantage of the expanded scope of the drug labeling.

Remember that FDA has the legal flexibility to approve certain new products that will be used in combination with others, even when cooperation is lacking. These products do not qualify as combination products under § 3.2(e)(3) because mutually conforming labeling that specifically cross-references the other product by brand is not necessary to ensure safety and effectiveness. Likewise, the Agency has the legal flexibility not to approve products where the requisite safety and effectiveness has not been established.

5. **How does the EU handle cross-labeling issues and products?**

EU does not have "cross-labeled" combination products. Indeed, we are not aware of any other jurisdiction in the world besides the U.S. that has "cross-labeled" combination products.

6. **What are examples of cross-labeled products?**

Below are examples that illustrate the difference between cross-labeled combination products and products with a concomitant use:

a. General use devices that deliver many drugs. The device label does not cross-reference a specific drug, and no drug label specifically cross-references the device. (Not a combination product as defined in § 3.2(e)(3); a combination product requires both of the combined products to specifically cross-reference the other.)

b. A device that is labeled for and specifically designed for the delivery of one specified branded drug, but although the drug labeling does not reference the device, the drug labeling does not conflict with and does not contraindicate the device. (Not a combination product as defined in § 3.2(e)(3); a combination product requires both of the combined products to specifically cross-reference the other.)

c. A drug and a device each with labeling that specifically cross-reference the other.

    i. One example here is a pen and associated pre-filled drug cartridges. Manufacturers then later seek and obtain approval for a new pen or a new cartridge that would be

used with the previously-approved companion product. (When the two products are first approved, they are approved as part of a combination product. But the follow on products are not combination products because they don't require the relabeling of the companion products.)

ii. A real-life example of this type of product is a photosensitizing drug and laser light source, such as Visudyne.[2]
    1) The Visudyne Drug Indications for Use specifically lists four laser systems that have been tested for compatibility with Visudyne and are approved for delivery of a stable power output at a wavelength of 689±3 nm, including the Zeiss VISULAS 690s laser and VISULINK® PDT adapter.
    2) The Zeiss VISULAS 690s laser and VISULINK® PDT adapter Device Indications for Use specifically state that the VISULAS 690s and VISULINK PDT are intended for use in VISUDYNE therapy as sources of photoactivation of VISUDYNE.
    3) The label also instructs the user to refer to the VISUDYNE Package Insert for information and instructions for the use of the drug and for information on laser power, duration and light dose

d. A drug and a device that are specifically identified in each other's labeling, but where only these products may be used together and there is no substitute for either one. (This is a combination product and would not be impacted by additional products coming onto the market.)

After you have had a chance to review our comments, we would very much like to hear your thoughts. If you would like to discuss, please contact me at: bthompson@ebglaw.com or (202) 861-1817.

Kind regards,

Bradley Merrill Thompson,

On behalf of the Combination Products Coalition

[2] http://www.visudyne.com/pub/hcp/.

APPENDIX A

Where Cross-Labeling Matters in the Regulation of a Product

This Appendix addresses where cross-labeling matters in the regulation of a product. In other words, what unique requirements does the cross-labeling category trigger? We have organized this Appendix by various types of regulatory requirements.

Type of Regulation	Impact
Registration and Listing	No impact – Each manufacturer is required to register and list as normal.
Pre-Clinical and Clinical Studies	We can think of no special or unique requirements. As with any product, the product claims and instructions for use will drive the design of a clinical study.
Submissions	We can think of no special or unique requirements. As with clinical trials, the product claims and instructions for use will drive the data that need to be included in a product submission.
GMPs	The combination product GMP proposed rule would not change the GMP requirements that apply to cross-labeled products. There are no unique or special GMP requirements that apply to cross-labeled combination products--the constituent parts of a cross-labeled combination product remain subject only to the GMP regulations applicable to that type of constituent part. Communication and interaction between the manufacturers of a cross-labeled product and the application of requirements such as change and purchasing controls. However, these requirements do not change by virtue of dealing with a combination product. Addressing GMP requirements as applied to a cross-labeling product may impact how certain requirements are implemented, but the implementation is simply an application of the existing requirements under the respective GMP schemes. Further, even with respect to change control, the information provided on approval is all that is expected because the quality system and vigilance is expected to continue to ensure compatibility. Examples of products handled in this way include concomitant devices like devices and other devices, and devices and drugs (general use drug delivery devices like pumps). None of these products require formal written agreements between companies regarding post-approval changes.
Adverse Event Reporting	The proposed rule on post-market safety reporting for combination products has suggested the following principles that would apply to cross-labeled combination products: • If there are two marketing applications for a combination product (e.g., an NDA for the drug constituent part and a PMA for the device constituent part), the product is subject to the reporting requirements under part 803 for the device constituent part, and to the reporting requirements under part 314 for the drug constituent part. • If there are two separate application holders, each applicant holder should comply with the postmarket safety reporting requirements associated with their respective applications. An applicant also must

Type of Regulation	**Impact**
	submit information received about an adverse event to FDA or the reporter for the other constituent part of the combination product. The other potential reporter then has to investigate and report the event in accordance with the statutory provisions and regulatory requirements for postmarket safety reporting for their constituent part of the combination product. Note, however, that these requirements are driven by the number of *applications*, and thus do not need to be driven by virtue of the product being cross-labeled.
Recalls	Because the products are distributed separately, a safety or quality issue requiring a recall should impact only one of the products. A limited exception would be a situation in which a safety issue could not be attributed to one constituent part of a cross-labeled product. In this case, both products would need to be recalled.
Drug/Device Identifiers	No impact – Because the products are distributed separately and are not combined, each product is still required to comply with any identifier requirements that apply to that particular product.
Interaction with the Agency	Being regulated as a cross-labeling combination product enables access to the Office of Combination Products and that Office's assistance with coordinating product review and discussion among the Centers.