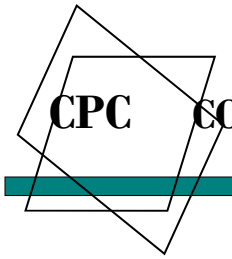

CPC COMBINATION PRODUCT COALITION

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January 11, 2006

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

Re: Docket No. 2005N-0098
Food and Drug Administration/Drug Information Association
Cross Labeling; Public Meeting; Combination Products and
Mutually Conforming Labeling

Dear Sir or Madam:

Through this letter, the Combination Products Coalition supplements its prior comments on the topic of cross labeling of combination products, filed on July 8, 2005. Since last July, the coalition members have continued to discuss the issues raised in the agency's request for comments, and we wanted to add some additional thoughts for your consideration. While we plan to continue to analyze these issues, and move toward some specific recommended solutions, in the interim, we wanted to convey these thoughts. Please let us know if you have any questions, or if you would like to discuss any of these comments.

We very much appreciate the thoughtful way the agency is proceeding in its analysis of the cross labeling issues, and the concern the agency is showing for developing the best approach for patients. We share that concern, and stand ready to help in any way that we can.

Very truly yours,

Bradley Merrill Thompson

Additional Thoughts on the Combination Product Cross Labeling Issue

1. FDA should not amend the portion of the regulation that defines the circumstances under which cross labeling of combination products is required (21 C.F.R. § 3.2(e)(3)) at this time.

We have thought long and hard about what the optimal approach to cross labeling should be, constrained in our thinking only by the existing statute. Our first goal, in that analysis, was to identify the best approach that protects the public health while encouraging innovation and the development of new technologies, leading to timely patient access. As a result of that analysis, we did indeed settle on an optimal approach. Next our analysis turned to whether the existing regulation would allow that optimal approach, or whether the regulation needed to be changed. While probably no regulation is perfectly written, we believe that 21 C.F.R. § 3.2(e)(3) already supports the approach that best achieves those goals. Below we outline (1) the optimal approach and (2) our analysis of the regulation.

a. The Optimal Approach

Last fall, we developed an approach to cross labeling that we captured in an algorithm. It is attached as appendix A. Although we originally wrote the algorithm to reflect what the current regulation requires, the CPC has spent considerable time reconsidering it, and concluded that the algorithm also reflects what in our view is the optimal approach, not just what the current regulation allows. Quite simply, we think it is the best way to assure the public health while simultaneously allowing innovation.

To explain how we developed this approach, we would like to map the final product back to what we consider to be the highest policy objectives in this area. Our logic flows from four policy objectives that we believe in quite strongly:

1. ***FDA should not play matchmaker between companies***. We suspect FDA agrees with us here. While there would undoubtedly be some benefit in companies working together, FDA mandating those relationships actually may stifle development. FDA's mission is to regulate products, and that is difficult enough without adding the task of "matchmaker" on top of it. Such activity would also be outside FDA's statutory authority.

2. ***The economic incentives that are most likely to lead to important public health breakthroughs are outside of FDA's control***. There will be times when people in government wish companies would develop products for which the existing market incentives are not enough (e.g., vaccine stockpiling). The government is familiar with those cases, and has systems and

organizations in place outside FDA to identify needs, create incentives and monitor progress. Those activities also are outside of FDA's mission and authority.

3. ***FDA must approve or disapprove the products as companies propose them,*** based on the evidence. That means some times the agency must disapprove a product (even though it may be technologically feasible) simply because the product is used together with another product, and there is no assurance that the two products will be used safely together in the future. That won't feel good to FDA personnel, because the product might (we don't really know this) be better if the two companies worked together, but FDA will have no choice as the regulator of product safety and effectiveness. That's not just the law; it is the right thing to do, given the goals stated above. When companies do not work together, there usually is a good reason for it, and that reason may not be known to the agency or for that matter to one of the product developers.

4. But ***FDA, importantly, does have flexibility under the law to weigh the risks***. Not constrained in our thinking by the regulation, we thought about the question: what is the best that FDA can do in this situation? To answer it, we focused on risk. FDA can't change the facts (because the public doesn't want them to play that role, as we outlined above), but we all want FDA to make the best decision, given the facts. Nearly all of FDA's decisions in fact are a weighing of the benefits against the risks. It is no different here. If a new device produces great benefits, but there is a safety issue created by a lack of coordination between two companies, FDA has to weigh that risk. If the benefits outweigh the risk, FDA has the flexibility to approve the product. In this whole paper, that is perhaps the greatest insight we can offer. FDA does in fact have the power to do the right thing. While the agency can only play the hand it is dealt, it does have the authority to play that hand to the best advantage of the patient—approving products that on a net basis offer greater benefits than risk. We can ask for nothing more.

Legal Authority for Reaching the Rick/Benefit Assessment

That is how the process optimally should work, and the existing statute and regulation permit it. A lawyer might reasonably ask: where in the statute is that authority? The wrinkle in the statute, that we are not sure FDA fully appreciates, is that to approve the product based on a weighing of the risks, FDA first must determine that the two products reflect concomitant therapies, ***and are not combination products as that term is defined in the law***. That last point bears repeating; the two concomitant therapies that FDA

assesses by weighing the risks are not combination products! FDA asks what discretion does the agency have to regulate combination products, and our answer is that FDA has great discretion, but it must first decide that the products at issue do not meet the legal test for combination products. The algorithm in appendix A explains the series of questions that must be answered to arrive at that conclusion.

Frankly, we see no disadvantage to that. FDA does not loose any important authority by that conclusion, and importantly it makes sense to reach that conclusion if FDA feels it should approve the products independent of any cooperation between the companies. Of course, one cannot have it both ways, in the sense that FDA may not say on the one hand that products can be safely used without any cooperation between the manufacturers and approve them on that basis, and on the other hand treat the products as combination products for other regulatory purposes. FDA must come down on one side of the combination product definition or the other, but that is as it should be.

Implications of this Approach

Candidly, we think FDA in a manner already employs this approach, although maybe not using these words or conscious of these choices. When FDA determines currently that "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", the agency in effect is deciding whether a form of cooperation between the parties (to ensure that labeling change is made) is required. Moreover, on the other hand, when FDA approves a drug delivery device that cross references a drug without requiring any evidence that the two companies are working together to address labeling and other coordination issues, the agency impliedly is deciding that cooperation is not necessary to approve the device. In that later case, the products are simply used concomitantly.

Bottom line: we are suggesting that the agency expressly acknowledge what it is already doing, which is already the best way to approach this situation.

To be honest, right now we are not sure what the agency considers when making those decisions. But we suggest that the agency communicate whatever those considerations are to the regulated industry, and our recommendations for what those considerations should include form the basis of our proposed risk assessment described in the appendix. We discuss in further detail the elements of the risk assessment in the next section.

To be blunt, this approach offers a lot of flexibility for the agency. We have heard the agency say in different forums that it wishes it could approve some important public health break-through products in the absence of cooperation between the parties. This gives FDA a framework for doing so. So long as FDA makes a conscious decision that cooperation is not absolutely necessary, even though a cross reference is made, it can approve the products without an agreement between the parties (subject to the limitations on the use of proprietary data.)

b. Assessing the Current Regulation

So, that is our ideal policy approach to cross labeling, and we next set about evaluating whether that approach is consistent with the existing regulations. We believe it is. In this regard, we focused on subsection 3 of the definition in 21 C.F.R. § 3.2(e), which provides that:

> A drug, device, or biological product packaged separately and 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.

In our July 8, 2006 comments, we offered a detailed assessment of the regulation, and concluded that the approach outlined above is indeed consistent with the regulation. As we observed above, probably any regulation could be improved, but we think the current version is good enough for now, and the benefit of any changes would be modest at best. In our July 8 comments, however, we did suggest that FDA publish a guidance document to clarify the agency's interpretation of the regulation. We will put together some materials that will help the agency with that task, should FDA elect to go that direction.

2. With regard to the risk assessment we recommended in our comments, it is important to note what kind of products would be excluded from the combination product category on that basis.

a. Overview of Risk Assessment

As already observed, most regulatory decisions are made on the basis of risk, and this is an example of where such an approach is certainly appropriate. In the preceding section we explained our approach: FDA can approve drugs, devices and biologics separately, despite cross references, without cooperation between the companies where the risk created by the lack of cooperation is relatively low compared to the benefit. In making that determination, at least three principles guide the process:

1. The benefit/risk balance must tip in favor of approval. The two sides of that balance must be considered together. The greater the benefit, the greater the risk that can be tolerated.
2. Like all decisions of this sort, this decision must be based on data.
3. The company, of course, has the burden to supply the data (if FDA does not already have such data in legally accessible form) and to prove the company's case.

None of that seems controversial. But the hard part is figuring out what the risk really is.

b. Specific Elements of the Risk Assessment

In our July 8 comments, we suggested some areas in which FDA might want to request data. They include:

(1) The likelihood that product A will be changed in the future.

(2) The consequences of possible changes to product A. Here we would be concerned with any special consequences unique to the combination, as opposed to consequences that would occur regardless of whether product A is used alone or with product B.

(3) The effectiveness of company B's ability to monitor product A for such changes.

(4) The ability of company B to effectively label the combined use without the need to relabel product A (which establishes that combination product status is unnecessary).

(5) Any other issues that bear on the ability of company B to assure the safety and effectiveness of the combined product in these circumstances.

This risk assessment would be provided to FDA in the submission seeking clearance or approval for product B. For example, it could be a section of a 510(k) or PMA.

The approach to conducting the risk assessment is reminiscent of a risk assessment used to consider the need for a recall. The company must pose a variety of "what if" questions to consider all of the possible things that could go wrong, and the effectiveness of possible preventative measures. Like a risk assessment for a recall, it will rarely yield a very specific quantitative assessment, because there will be a variety of unknowns that require speculation. Also as with a recall risk assessment, the company will need to use conservative assumptions. For example, it will need to assume worst case scenarios when predicting adverse health effects of product changes. Thus, the assessment will tend to overestimate the risk in the face of uncertainty, but that is how it should be. As already noted, the burden of proof is on the company, not the agency.

c. Risk Assessment in Practice

How often will the risk assessment allow FDA to approve a product in the absence of cooperation? That's hard to predict, but we can see a few circumstances where it will most likely be useful. They include:

1. The drug at issue has been around for a while, is well understood and not likely to be altered.
2. Low risk products where an adverse events, and particularly a malfunction, are not likely to produce death or a serious or life threatening outcome.
3. There exists a significant benefit to the unapproved product over and above currently available alternatives.

The first two situations may not be very interesting to FDA, but frankly, that's not a limitation of the proposed risk assessment; it's just reality. Proceeding without coordination between the parties when a drug is new and the risks associated with the use of the products are great would, in fact, in many instances, create material risk that would have to be outweighed by a clear showing of substantial benefit. That can happen, and is our third category, but it does require solid data showing clear benefit.

That is the good news. FDA can proceed to approve the product if the public health benefit will be substantial enough to outweigh the risk. Psychologically, the agency won't like to be in that position because the benefit is the result of science and the risk is the result of human decisions. However, we frankly don't expect that dilemma to come up very often because if the benefit is that great and that certain, cooperation between the two companies is likely to exist. As stated in our earlier comments, there are many reasons for non-cooperation, and a common one is where the public health benefit is uncertain or insubstantial in the view of the company with the existing product. Where the benefit is certain and substantial, cooperation is much more likely.

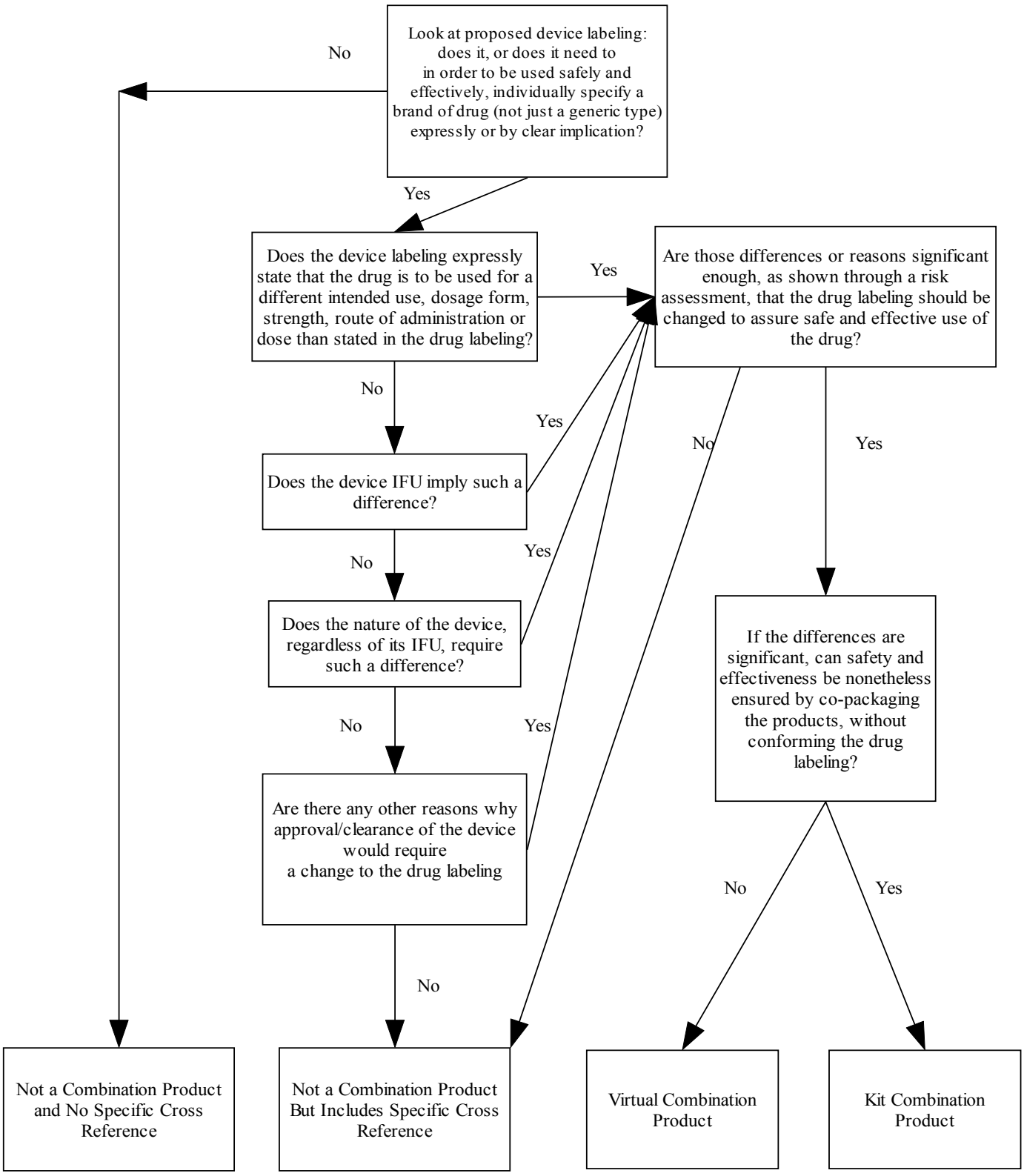
But, at the end of the day, this is and must be FDA's framework for making the decision of whether or not to approve a product without an assurance of cooperation. FDA must

weigh the risk created by a lack of cooperation, informed by data, against the public health benefit of the new product.

3. The flow chart in Appendix A that we have wrote for the drug delivery device scenario applies equally to other combinations.

Initially we developed the flow chart that follows in Appendix A for the drug delivery scenario. Now that we have had time to reflect on it, and mentally apply it to different scenarios such as a drug/biologic combination, and a biologic/device combination, we believe the principles embedded in it apply equally to other situations just as well, although the vocabulary obviously would need to change.

Appendix A: Flow Chart for Determining Whether a Drug and Device Represent Virtual Combination Products



Regulatory Consequences of the Combination Product Determination

Category (taken from pervious flow chart)	Not a Combo Product and No Specific Cross Reference	Not a Combo Product But Includes Specific Reference	Virtual Combo Product
Is an agreement between the parties assuring coordination required to approve the device?	**No**	**Maybe**. If a specific reference is made by brand, an agreement may or may not be necessary, depending on a risk assessment The risk assessment would be prepared by the firm seeking the second approval (company B), without the cooperation of the other company (company A). This risk assessment would consider and address such issues as: (6) The likelihood that product A will be changed in the future. (7) The consequences of possible changes to product A. Here we would be concerned with any special consequences unique to the combination, as opposed to consequences that would occur regardless of whether product A is used alone or with product B. (8) The effectiveness of company B's ability to monitor product A for such changes. (9) The ability of company B to effectively label the combined use without the need to relabel product A (which establishes that combination product status is unnecessary). (10) Any other issues that bear on the ability of company B to assure the safety and effectiveness of the combined product without the	**Yes**, an agreement between the two companies is required to assure that product and labeling changes are coordinated, including the initial relabeling of the drug to make conforming changes

		cooperation of company B. This risk assessment would be provided to FDA in the submission seeking clearance or approval for product B. For example, it could be a section of a 510(k) or PMA.	
Is a right of reference to the drug file required to approve the device?	No	Maybe	Yes, because the labeling of the approved drug will need to be changed, so the issues go beyond the mere safety and effectiveness of the device alone.
Claim support	Must be able to support all claims in labeling, including any claim that the device enhances the safety or effectiveness of the drug. Being able to support a claim means having the data in hand, or having permission to reference data owned by another.	Same	Same
Should the approval be conditioned on anything?	No	Maybe	Yes, on conforming changes to the drug labeling
What authorities can FDA use after approval?	Drug for the drug and device for the device	Same	Same