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President

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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:

Thank you very much for organizing the meeting in collaboration with the Drug Information Association on May 10. The attached document outlines definitions and proposals for addressing the broad range of products the fell into the overall area of "cross-labeling" addressed at the meeting.

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## Introduction

Part 3.2.e(3) defines a type of Combination Product where the two components of the product are packaged separately. There are two elements to this definition which must be in place in order for this to be a Combination Product rather than just two products, separately regulated, that work together. In order to be a Combination Product, the regulation states that BOTH products must be required to achieve the intended use, indication or effect AND that the approval of the proposed product will necessitate the labeling of the approved product be changed. There are multiple situations, all of which need the two products to have labeling that is consistent. However, the level and depth of the labeling uniformity and cross specificity is not always the same and not all of these combinations should be regulated as Combination Products.

The first section below proposes several definitions that describe different types of labeling to address the different relationships for two products that can be used together. The second section explores examples of these product types and proposes methods of regulating them.

## Definitions

### Combination Product

Part 3.3e(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;"

### Cross-Labeling

"The labeling of each of two individual, separately marketed products which have no approved function or use without the other product and where the products specifically require the use of the other Branded products."

In these cases the labeling of each would specify use with only the Branded complementary component of the combination.

This type of labeling would be required when it is determined that the use of other drugs or biologics for the same therapy (even a generic equivalent) or other devices (even those that meet the same set of specifications) would not result in the same level of safety or effectiveness. This may also be used where the lack of cooperation between the two companies makes access or control of one set of specifications problematic. These products would meet the definition of Combination Products under Part 3.2e(3).

### Mutually Conforming Labeling

“The labeling of each of two individual, separately marketed products which have no approved function or use without the other product where labeling of each product is consistent with and does not contradict, or specifically contraindicate the use of the other.”

The products best suited to this definition are those where it would be feasible and practical to establish a set of individual specifications or tests that would assure the continued compatibility of the two components. This would allow for the innovative development and substitution of equivalent devices and/or drugs (generic or equivalent biologics) without excessive regulatory restrictions and duplicative filings. In most cases these products would meet the definition of a Combination Product, however in some instances this could change after the initial approval of the two products (See examples below).

Note: This comment proposes that this, rather than cross labeling, be the default labeling method for combination products meeting the requirements of Section 3.2e(3).

### Labeled For

“The labeling (or promotion) of one product for use with a Branded, individually specified drug, device, or biological second product, for which the first product is solely indicated.”

For these products, the Branded product does not specifically call out the “Labeled for” product or even any specific or branded concomitant product. It may not even call out the use of the product at all, but does not specifically contraindicate against it. This differs from the mutually conforming labeling in one of two ways. The first is the case where the second product is already approved and marketed (for use with another equivalent product); therefore its labeling would not need to be changed. The next situation would be if the second product was already marketed alone without requiring any concomitant product, that is it did not need the new product to achieve its intended use.

These products do not meet the definition of a Combination Product as they may not BOTH be needed and the approved labeling of one may NOT need to be changed.

### General Use

This is a potential evolution for many of these devices when their use with the drug becomes routine standard of care and/or different brands of devices that can achieve the same intended use with the branded drug become available; or the drug becomes generic.

## Specific Situations

### Cross Labeling

As stated above, this type of control should be required when it is impossible to establish a set of individual specifications, tests or requirements (which could possibly include some clinical verification) that would assure the continued compatibility of these products. (If these requirements can be established, then the products should be considered for mutually conforming labeling as detailed below.) A critical inference drawn from this type of relationship is that the release of one product must be tied to the release of the other. In order to assure that the products remain consistent, even though they may be manufactured and distributed separately, they must be covered under one premarket approval. That would assure one “owner” or sponsor who would be responsible for the combination. Even if the “second” product is manufactured by a different company, the individual ownership would assure one point of responsibility and control. GMPs/QSRs would require a written agreement and assure cooperation. In this case, all post market changes would also be submitted and approved against one approval file, owned by the sponsor. If possible it would also be beneficial if these products could be distributed together to assure proper use.

This situation would also apply to drug/device implementations that would require a new formulation, concentrations, primary container or some other modification to the drug manufacture for a new delivery method. In this case the Brand drug company would either cooperate, or the delivery company would need to file an NDA under 505(2)(b). In either case, one company would be responsible for the combination.

A slightly different situation would be when a new device proposes to **change ONLY** the labeling for an approved drug or biologic (e.g. the route of administration, indication, population or even a contraindication). This situation would not apply if the labeling is not so specific such that the new route of administration, dosing, etc. is not in conflict with the existing labeling. These products would fit the “labeled for” definition. However, if the labeling must change, then these products meet the definition of, and should be regulated as Combination products. If the companies agree to cooperate, then these products should be controlled as suggested above (when it is impossible to establish a set of individual specifications or tests that would assure the continued compatibility of these products) with a supplement to the NDA of the branded drug or biologic to change drug or biologic labeling and approve the device and the combination. If there is no cooperation, the solution as to how to control these products is more problematic, as the FDA does not have the authority to require the drug manufacturer to cooperate with the device manufacturer, or the authority to force the drug manufacturer to change their labeling. One solution that should be considered when there is no cooperation between the companies would be for

the device manufacturer to file an NDA under 505(2)(b). Further discussion of this option is included below.

### Mutually Conforming Labeling

This type of control should be the default for all combination products that meet the definition of Combination Products in Part 3.2e(3). In these situations, the combination is required to achieve the therapeutic effect AND the labeling of both must be changed (or initially approved). The unique nature of these combinations is that in many cases, once the two products are on the market, the marketplace can develop alternative devices to work with the novel drug, or even find other drugs that can be used with the novel device. In these cases, the second-to-market device or drug would NOT meet the definition of a Combination Product as the labeling of the currently marketed concomitant product would not need to be modified.

Some examples are:

- Inhaled drugs for use with a nebulizer
- Drug for Infusion (not prefilled) that require a specialized infusion pump (i.e. PCA pump, insulin pump, implantable pump)
- Cartridges that require a specialized injector that are not supplied pre-filled (e.g. insulin, growth hormone)
- Drugs that require a specialized IVD to select patient population or to monitor dosing. (e.g. Herceptin/Her-2/neu)

Once these products are approved, they could easily move into the next class of products, which by definition are no longer considered Combination Products. This evolution will be the result of innovation, mostly on the part of device manufacturers to find more efficient, easier, better products to work with the now approved drug without requiring a change to its approved labeling. This can only be true if the default for these products is “mutually conforming” without specifically calling out each other by brand.

The submissions for these products would initially be coordinated but should be discrete (e.g. embedded 510(k), NDA/PMA), to establish the potential for evolution after approval/clearance. The coordinated approval/clearance of two separate submissions would assure post marketing regulation appropriate to a set of products that are truly a separate device and a drug or biologic.

## Labeled for

### Examples:

- A Branded drug in a prefilled syringe and an auto injector specifically designed, labeled and manufactured for that product (Avonex Auto-injector).
- A Branded drug indicated for subcutaneous or IM injection (for use with standard general syringes) and an needle-free injector specifically designed, labeled and manufactured for that product (SeroJect; CoolClick)
- A Branded drug indicated for infusion (for use with standard general use infusion pumps) and a pump specifically designed, labeled and manufactured for that product) (Lutrepulse pump; OR pump).
- A Branded or Generic drug with very general dosing, route of administration or intended use and a new delivery device (micro-oration type device or insulin pumps).
- All of the examples in mutually conforming labeling once there are more than one device that can deliver the Branded Drug or drug that uses the approved IVD or device

## General Use

General use delivery devices are specific devices that are sufficiently flexible, or can be easily modified to adjust for the different drug or biologic delivery requirements. These may start out as mutually conforming products or even cross-labeled products that are generalize as they evolve and are accepted as part of the standard tools used by the practitioner for the delivery of drugs and biologics. The same can be applied to IVDs that may have one use initially, but are discovered to have predictive value in several disease or drug dosing situations.

## **Special Discussions**

Several issues require additional discussion. The first area are those products that are unique in as much as their initial approval is as 3.2e(3) Combination Products (Mutually Conforming labeling) which through innovation and/or establishment as standard of care allow the development of “Labeled For” follow-on products which no longer meet the definition of Combination Products. The second are Medical Devices that are developed that “expand” the use of approved Branded drugs.

## Combinations Products Through Initial Approval

There are a unique set of products (mostly drug-device and drug-biologic, but it could be foreseen that drug-biologic combination could also fit in this category) that are classified as Combination Products due to their interdependence in order to achieve their therapeutic indications. All of these products are sold separately, so they are Combination Products by virtue of their labeling and Section 3.2, however the primary reason these products are classified in this manner is they must be approved concurrently.

Even if these exact drugs and devices existed for some other purpose (not just an expansion of a general intended use as for syringes and infusion pumps) they would necessarily need to have their labeling changed to be part of the new combined indication.

Examples of these types of products are Drug/IVD combinations, where the drug dosing is defined by the results of an IVD test (Herceptin/Her-2/neu), Drugs for inhalation that are delivered by nebulization, Drug Cartridges that require and Injection Pen and Needles, Light activated drugs and their lasers, Anesthetic drugs and Microportation devices,

There are several factors that make these products unique

1. They are co-dependant - Each product has no (or a different) intended use without the other
2. They are sold and distributed separately
3. For the most part,
  - a. they include reusable devices and single use drugs
  - b. The device technology exists, but must be modified or specialized to work effectively with the drug,
  - c. The device function/output can be sufficient specified, verified, controlled and assured with in-vitro testing to assure continued compatibility, for the most part without significant additional clinical studies.

Most importantly, once marketed, additional devices and possibly drugs (in the case of combination with IVDs), could be developed and approved as separate drugs or devices. Under a flexible reading of the regulation, these would no longer be combination products.

This is a reasonable interpretation and would suggest that these are concomitant products and only Combination products by nature of initial approval and timing. Consideration in this manner will allow for cooperative initial development, but also for competition, innovation and advancement once the drug or device is approved.

Drug/Biologic combinations with IVDs present a unique case. The IVD that identifies and quantifies and analyte with no predictive or diagnostic value can be marketed as an ASR. However, once a drug intends to use this analyte to define a treatment population or on which to base a dosing, then it must be registered as a Medical Device. In this case these must be approved together. This precedent for this is for two submissions (NDA or BLA and PMA or 510(k)) where the review and approval are coordinated to assure that the approval happens at the same time so as not to force the FDA to approve a product that cannot be used. However, once approved, the market place will generate equivalent

devices that identify the same analyte with equivalent or better consistency, accuracy or specificity. These can be labeled to be used with the drug without affecting the labeling of the drug. Therefore, by definition, these are devices and not Combination Products. In addition, there may be additional drugs that are developed, or new intended uses for existing drugs, where the analyte (and the IVD) prove to be required to assure identification of the treatment population of assure proper dosing. In this case the labeling of the IVD would not need to be changed and this would also not meet the definition of a combination Product.

This scheme does not preclude the generation of appropriate pre-clinical and/or clinical data or the collaborative review of these new products, but does define them separately as medical devices or drugs/biologics regulated according to the appropriate authorities

#### Combinations That Modify Drug Labeling Only

As stated in the definition of cross labeled products, when the Branded drug company does not choose to cooperate with the device company proposing the new delivery mode, a novel approach is required. It seems that this situation fits directly within the intent of the Hatch-Waxman amendments to the Act which were intended to encourage innovation without creating duplicate work and to reflect the same principle as the 505(j) application. That it is wasteful and unnecessary to carry out studies to demonstrate what is already known about a drug. It is specifically for situations like the above where a right of reference does not exist to the innovator's NDA. Although this has only been used to reference the pre-clinical and clinical studies that support the safety and efficacy of the drug, this should be expanded to include the CMC section in cases where there is no change to the drug, only to the labeling. Therefore the submitter of the 505(2)(b) application would rely on the FDA approval of the drug, including the clinical studies and the CMC. The only additional information would be the new packaging, labeling and any studies to show the safety and efficacy of the new use.

One issue that this path raises is Patent Certification. As the 505(2)(b) process assumes that the new company will manufacture the drug on their own and therefore infringe on the patents of the innovator, this would not be the case in these instances. Since in these instances the drug would not be modified, only the labeling, the innovator company would maintain ownership of the product, its manufacture and sale, but not its final use for this application. Since the only source of the drug would be from the innovator, they would still have commercial exclusivity and be assured profit from all sales. Also, since the delivery company is the sponsor for the 505(2)(b), they would be responsible for the continued testing, certification and release of the repackaged drug for that indication. Their GMPs and Quality System would require the appropriate control of the supplier (Branded Drug Company) which could include written agreements, inspections, certifications, incoming testing, etc.

This proposal has not been subjected to a comprehensive review of the legal issues involved with this route, but it is an avenue worth exploring to assure continued innovation in drug delivery. If this path survives legal scrutiny, it will assure availability of innovations designed to reduce the potential toxicity through targeted and efficient dosing. It would also be an extremely efficient way to expand the indications and uses for drugs that are already developed, approved and marketed. If it does not, it should be considered as an expansion of the generic law through congressional action.

### **Conclusion**

This comment outlines different labeling and regulatory solutions to products that are distributed separately but are used together. These products can have significantly different relationships, some that can even change over time such that one solution will not be adequate. The labeling definitions and schemes proposed will help address these diverse relationships. Except for the final situation above, all of these can be implemented through guidance and interpretation, without any legislative or regulatory changes. Even these definitions and situations may become obsolete or may not cover the technological advances which at this time we cannot even comprehend. However, it is a good start that is worth consideration as it will address most of the current situations.