

# The Combination Product Problem



By Michael Gross, PhD, RAC

This is the first in a series of articles that focus on the complexities of regulating combination products. The purpose of this first article is to establish a basic framework for discussion of the problems associated with the development, registration and marketing of combination products and how they may be addressed.

Combination products are a distinct category of medical products along with drugs, biologics and medical devices.<sup>1</sup> The US Food and Drug Administration (FDA) may apply any regulatory resource it deems necessary to regulate a combination product.<sup>2</sup> For example, to regulate a drug-device combination product, FDA may apply drug or device regulations or both in an effort to assure the safety and effectiveness when these two constituent parts are combined. It is unclear how FDA determines how and when to apply more than one regulation to regulate a specific aspect of a combination product. Only a small number of regulations and guidances explain how the predicate rules for drugs, biologics and medical devices are applied to regulate a combination product. Much is handled on a case-by-case basis. For example, FDA has specified in some combination product Premarket Approval Application approval orders how certain postapproval compliance requirements should be handled. FDA<sup>3</sup> has also approached certain combination product problems on a class basis. A recent draft guidance and companion document on coated cardiac stents from FDA's Center for Drug Evaluation and Research (CDER) and Center for Devices and Radiological Health (CDRH) describe approaches to labeling, biocompatibility, application content and reporting manufacturing changes for these products.<sup>4</sup>

What constitutes a combination product is not completely clear and, given the potentially large number of combination products that can result from combining different medical technologies, it is difficult to develop broad principles on how regulate them.

## Definitional Problems

Combination products are formed when two or more medical product constituents are combined in a way that fits the legal-regulatory definition of a combination product.<sup>5</sup> FDA's product jurisdiction regulations describe four types of combination products. But not all of the definitions are clear. The first combination product type, unofficially termed a "single entity combination product," results when two or more different medical products are combined and produced as a single entity (e.g., a pre-filled syringe or a coated stent).<sup>6</sup> The second is produced when two or more different medical products are co-packaged as a single unit or in a single package.<sup>7</sup> This type has become unofficially known as a "kit combination product."

A third type of combination product, the one with an unclear definition, results when "[a] drug, device, or biological product [is] 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..."<sup>8</sup> This combination product type has become unofficially known as a "cross-labeled combination product." The use of this term adds to the confusion over this definition. The unofficial name and the regulatory definition suggest that a combination product is formed when two separate products have labeling that is mutually conforming, wherein the labeling of the constituent parts refers to specific use of the counterpart constituent. However, this interpretation is not established in any official FDA proclamation. The cross-labeling issue is one of the oldest combination product problems. FDA's Office of Combination Products and its predecessors have been working for some time to clarify the question of what constitutes cross-labeling.<sup>9</sup> But, what is meant by cross-labeling



and what the regulatory definition described in the Product Jurisdiction regulations means remain unclear.

A fourth combination product type results when the proposed labeling of a separately packaged investigational medical product indicates that it is intended for use only with another individually specified investigational medical product, and both are required to achieve the intended use, indication or effect.<sup>10</sup> From a legal-regulatory point of view, it may be important to define this type of combination product. But, other than its distinction as involving two or more investigational products, this product simply represents a subset of the other three combination product types and does not merit further discussion here. Thus, only three types of combination products will be discussed in this series of articles: single-entity, kit and cross-labeled.

### Too Many Possible Combination Products

We usually think of combination products as resulting from the combination of two different medical product types. But combining three medical product types is also possible, and the incidence of this type of combination product is likely to increase. “Triple combination products” can arise through the combination of two or three different medical product constituents. For example, combining two different kinds of medical products with a third medical product that is the same type as one of the other two still produces a triple combination product. And, there is more than one way to combine the constituent parts. For example, two medical product types may be combined into a single entity and the third constituent part may be combined through cross-labeling. The biologic-device combination product, Peg-Intron Pen, is cross-labeled for use in combination with the drug Rebetol. This is an example of a biologic-device-drug combination product.<sup>11</sup>

Given that there are three basic ways to combine medical product constituent parts (forming a single entity, through co-packaging and through cross-labeling), and given that there are three individual medical product types (drug, biologic and medical device), there are nine possible ways to combine them. However, when only like medical product types are combined, they do not produce a combination product. So that leaves six basic double combination product types, if primary mode of action is not considered.<sup>12</sup> However, considering the primary

mode of action of a combination product, which determines the agency component with primary jurisdiction for a combination product, there are actually twice that number of outcomes resulting from the combination of two medical product types. So, 12 double combination products are possible.

Triple combination products may be formed when three different types of medical products are combined. As mentioned above, these can also be formed when two of the same type of medical product are combined with a different type (e.g., surgical kits may contain two medical devices and a drug product). Considering both the three different ways that the combination can occur and the influence of the primary mode of action, the potential number of triple combination product types is quite large. So a one-size-fits-all approach to the regulation of combination products is not practical. There are too many ways that a combination product can be formed and numerous predicate rules that may pertain to the constituent parts.

### Downstream Issues

One source of combination product problems is the potential for concurrent application of very different regulations. Uncertainty as to how to apply these regulations can arise during product development, during the marketing approval or clearance process, or after product approval. These are referred to as “downstream issues.”<sup>13</sup> FDA calls them postmarketing issues but some may arise prior to marketing. Five of these downstream issues will be discussed in forthcoming articles in this series. They are: structuring applications, structuring labeling, reporting change, safety reporting and quality systems.

### Applications

In September 2005, the Office of Combination Products issued a concept paper for public comment concerning the number of applications that may be filed for a combination product.<sup>14</sup> No regulation or guidance has followed the release of this advice on combination product submissions. The paper suggests that in most cases a single application is sufficient for a combination product but there are exceptions. No advice is provided on the format and content of these applications. A future article will discuss how to decide whether to file one or more applications for a particular combination and how to structure the content of these applications.

## Change

The rules for reporting changes to drug, biologic and medical device applications are all different. Once the number, format and content of an application or applications for a combination product are established, how are manufacturing changes to be reported? In particular, if a single application is filed following jurisdictional considerations suggested in the concept paper (e.g., if regulated primarily by CDER, a New Drug Application should be filed for marketing approval), how should a change to a constituent part with a secondary mode of action be reported? Suppose two applications are filed for a cross-labeled combination product. Is it necessary to coordinate the reporting of a change if the change only occurs in one of the constituent parts? If not, how are the overall safety and effectiveness of the cross-labeled combination product to be assured? Questions related to reporting of changes to applications and why this reporting may depend on application structure will be discussed in a forthcoming article in this series.

## Labeling

The way in which labeling of a combination product is structured depends in part on the structure of the application(s). When two separate medical products form a single entity combination product, separate labels typically result. But labeling is less clear for kit combination products. For example, interim FDA guidance suggests that convenience kits composed of marketed products may not require additional labeling.<sup>15</sup> But, how to label other combination products that result from co-packaging is not well defined. Combination product labeling issues will be discussed in this series.

## Safety Reports

FDA issued a concept paper on safety reporting for combination products in 2005.<sup>16</sup> No regulations have followed, but the issuance of a proposed rule on this subject has been anticipated for some time.<sup>17</sup> The rules for safety reports for drugs, biologics and medical devices are all different. The concept paper suggests that, generally, the approach to safety reporting should flow from the application type and jurisdictional responsibility for a combination product. For example, for a combination product with a device primary mode of action, Medical Device Reporting would normally apply. A discussion of how to file safety reports for combination products in the absence of defined regulation will be featured in a future article in this series.

## Quality Systems

The promulgation of new regulations for combination product quality systems is also anticipated.<sup>18</sup> FDA published draft guidance on this subject in 2004.<sup>19</sup> The draft guidance suggests that when the constituent parts of a combination product are physically brought together, compliance with more than one quality system regulation may be necessary. The current Good Manufacturing Practice standard for drugs and biologics is quite different from the Quality System Regulation for devices. But the draft guidance suggests that by supplementing one quality system with certain elements from the other, a quality system for a combination product may be constructed. Until a proposed rule for combination product quality systems is issued, the draft guideline is the only advice available from FDA on this important topic. This series will cover designing a quality system for combination product in the absence of a final quality system regulation and guidance for combination products.

## Summary

The regulation of combination products is complex and problematic due to the large number of possible product types and the multitude of regulations and guidance principles that can be applied. In a nutshell, the problem is determining when to apply to a combination product existing regulations and guidances originally intended for its constituent parts. The murky regulatory framework for combination products is slowly clarifying. In the meantime, companies must carefully consider the various regulations that pertain to the constituent parts of a combination product (i.e., predicate rules) and, in the absence of regulation and guidance from FDA, judiciously apply them. This series of articles will attempt to stimulate thought and dialog and provide advice on these important and complex issues.

## References

1. *Safe Medical Devices Act* of 1990.
2. 21CFR3.1.
3. Conditions of Approval stated in attachment to PMA Approval Letter dated June 16, 2006 to Orthovita, Inc. for Vitagel™ (P05044)
4. *Guidance for Industry: Coronary Drug-Eluting Stents-Nonclinical and Clinical Studies*. US Food and Drug Administration, Center for Devices and Radiological Health, Center for Drug Evaluation and Research (March 2008).
5. 21CFR3.2(e).
6. 21CFR3.2(e)(1).
7. 21CFR3.2(e)(2).



8. 21CFR3.2(e)(3).
9. Transcript of an FDA/DIA Workshop: "Combination Products and Mutually Conforming Labeling." (10 May 2005).
10. 21CFR3.2(e)(4).
11. A convention that will be used in this series of articles is that the combination product constituent part with the primary mode of action (PMOA) will be capitalized and mentioned first when specifying a combination product type (e.g., drug coated cardiac stents are Device-drug combination products).
12. The terms double and triple combination products are not official FDA terms, but are used to provide clarity in these articles.
13. The term downstream issue is the author's term and not officially used by FDA. It differs from a combination product postmarketing issue in that it may occur during development, product approval or postmarketing.
14. "Number of Marketing Applications for a Combination Product." US Food and Drug Administration, Office of Combination Products (September 2005).
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**Author**

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



  
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