Combination Product Terminology

By Michael Gross, PhD, RAC

This article is the second in a series concerning the complexities of developing and regulating combination products. It attempts to establish terminology conventions for combination product discussions to bring some order to an area that is fraught with misuse, which adds confusion to an already complicated subject.

Only a handful of established terms for combination products are in consistent use. A few terms are established in laws and regulations. Over time, others have found their way into usage and some of these are embraced by the US Food and Drug Administration (FDA). More are needed to communicate effectively and precisely about this complex topic, both internally and externally.

The use of certain terms is suggested in this article. These may or may not be accepted by FDA and should not necessarily be used in official regulatory communications. Still, they may be useful in other communications to present complex concepts in a clear and succinct way. Terminology that is codified in FDA's legal-regulatory framework or used in the agency's combination product communications will be initially be presented in bold type. Author-recommended terminology or conventions used in this article will be first presented in italics.

Combination Product Types

The term **constituent part** refers to the different medical product types that may comprise a combination product. *Double combination products* are formed when two different constituent parts are integrated to form a **single-entity combination product**. Similarly, **kits** are formed when two different medical product constituent parts are packaged together in some way. And a **cross-labeled combination** is formed when medical product constituent parts are presented separately but are connected to each other through labeling.[1] The term **type** can be applied to both medical product type (drug, biologic or device) and combination product type (single-entity, kit, cross-labeled).

Triple combination products are formed by combining as a single entity, as a kit, through cross-labeling or through a combination of two of these methods, three constituent parts—at least two of which are different medical product types (i.e., drug, biologic, device). A triple combination product is not esoteric; some exist today[2] and more are coming. Since a basic challenge of combination products is how to apply existing regulations originally intended for individual medical product constituent parts, the complexity associated with triple combination products is greater than that of double combination products.

Combining two drugs does not produce a combination product; rather, a **fixed-drug combination product** is formed.[3] Similarly, when two biologics or two medical devices are combined, a *noncombination product* is formed. But when a noncombination product is combined with a medical product constituent part of a different type, a triple combination product is formed.

Product Jurisdiction

Determination of which FDA center has **primary jurisdiction** for the regulation of a particular combination product is based upon its primary mode of action and this is dependent on its intended use**.** An *assumed*, *informal* or *formal* (through the submission of a **Request for Designation** to the Office of Combination Products) **jurisdictional determination** identifies the FDA center with primary jurisdiction for the regulation of a combination product (i.e., the **Lead Center**). If jurisdiction over a particular combination product lies with the Center for Drug Evaluation and Research (CDER), this does not necessarily mean that the product will only be regulated as a drug.

Similarly, if the Center for Devices and Radiological Health (CDRH) has primary jurisdiction, it does not mean that the combination product will be regulated only as a device. The FDA center with primary jurisdiction can apply whatever regulations it deems necessary to assure the safety and effectiveness of a combination product. To state that a particular combination product will be regulated solely as a drug, device or biologic is incorrect and confusing.

When describing combination product types, to signify the primary mode of (and therefore signify which center will have primary jurisdiction) it is suggested that the constituent part with the primary mode of action be stated first. Hence, a *drug-device combination product* is composed of a drug constituent part and a device constituent part and has a drug primary mode of action (e.g., a drug prefilled syringe). A *device-drug combination product* has a device primary mode of action (e.g., a drug-coated catheter).

Some medical device companies may have become accustomed to being regulated by CDRH. When developing technology platforms that may form the basis of a combination product, they may be concerned about the possible involvement of an additional FDA center (e.g., CDER) in a secondary role in the regulation of their new product. Ways to avoid having a new product regulated as a combination product may be considered. The outcome depends in part upon product presentation, intended use and if the product fits the regulatory definition of a combination product.[4] When combining medical product technologies to form a platform, different presentations are possible. Based upon intended use, a particular technology platform can be designed as a standalone medical device intended for *concomitant use* with a drug or biologic, where one or both are not specifically labeled for use with the other.[5] Such a device might be considered as a noncombination product. Alternatively, by physically integrating or co-packaging the different medical product constituent parts, a combination product

is formed. The cross-labeled combination product is the least-clearly defined of combination product types and this may provide some flexibility. Avoiding designation as a combination product begins with keeping the constituent parts separate, carefully considering product claims and presenting the product accordingly.

Clinical Development

The clinical development of a drug or biological product takes place in **phases**. In simple terms, **Phase 1** clinical development focuses on safety in human subjects, usually normal volunteers. **Phase 3** studies, conducted in patients, are intended to provide clinically and statistically significant proof of effectiveness and sufficient clinical safety experience to define labeling claims and establish the benefit/risk ratio. **Phase 2** clinical studies are conducted in patients and serve as a bridge between Phase 1 and Phase 3 studies. They address dose ranging/response, pharmacokinetics, and preliminary safety and effectiveness, among other issues.

Medical device development follows a different paradigm. It seems improper and it is potentially confusing to use the terminology describing drug development for device development. The author prefers to describe device development as taking place in ***stages*** rather than in phases. *Stage 1* is a term used to describe early (i.e., crude or surrogate) medical device prototypes (rather than clinical studies) used in feasibility and proof of concept studies and/or safety evaluations of device technologies. *Stage 3* describes late-stage (i.e., fully developed) design prototypes that may resemble or be identical to the market image. The development of *Stage 2* medical device prototypes will fall between the early Stage 1 and later Stage 3 prototypes, and is where the evolution of a medical device's design primarily occurs.

Regardless of type, the clinical development of a drug and device containing combination product involves the mixing and matching of different product prototype stages (i.e., Stage 1, Stage 2 or Stage 3) with different phases of the clinical development (i.e., Phase 1, Phase 2 or Phase 3). When such a combination product enters a Phase 1 clinical trial, in terms of its device prototype, it may be at Stage 1 or 2. When pivotal clinical studies are being conducted, the prototype is likely to be at Stage 3.

Conclusion

Future articles in this series will consider complexities associated with the development and regulation of combination products. The author refers to these issues as *downstream issues* since they occur downstream of jurisdiction and concern the development, registration and marketing of combination products.

References

1. Exactly how this occurs is not clearly established. See FDA/DIA Cross Labeling Workshop: Combination Products and Mutually Conforming Labeling (May 2005).
2. Schering-Plough's INTRON® A for Injection, in multi-dose pens, is a single entity combination product) which is cross-labeled with REBETOL® (ribavirin USP) and is a triple combination product.
3. 21 CFR 300.50.
4. 21CFR3(2)(e)
5. FDA's position on this type of product is evolving. See FDA's *Draft Guidance for Industry: New Contrast Imaging Indication Considerations for Devices and Approved Drug and Biological Products* (September 2008).

Author

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