PHARMACEUTICAL ONLINE

Guest Column | September 20, 2019

Analyzing FDA's Draft Guidance On Premarket Review Of Combination Products

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Few could have predicted the impact of combination products on the global pharma and biotech marketplace. Over the last decade the FDA has responded to the widespread adoption both organizationally and from a policy perspective, providing a road map for industry to effectively navigate the regulatory nuances combination products present. Today the FDA provides a structured framework for evaluating combination products, considering both device and drug component contributions to industry. In the European Union, things were similarly structured with drug sponsors approaching the appropriate regulatory agency or notified body based on the type of product they intended to put on the market. However, with the escalation in sophistication and capability of novel delivery systems, regulators on both sides of the Atlantic risked falling behind when combination products did not fit neatly into their regulatory paradigms.

The new EU draft guidance, *Guideline on the quality requirements for drug-device combinations,* and U.S. draft guidance, *Principles of Premarket Pathways for Combination Products,* are the latest attempts by each body to adequately regulate combination products. In this two-part series, we examine the two guidances in detail. Part 1 covers the U.S. regulatory guidance, and Part 2 explains the differences in European Union guidelines for combination products.

Principles Of Premarket Pathways For Combination Products Draft Guidance (U.S.)

In the United States, a combination product is a product comprised of two or more regulated components (constituent parts) that include drugs, biologics, and medical devices.[1] Three categories of combination products are defined by the relationship between the constituent parts.

1. Single Entity: physically, chemically, or otherwise combined or mixed and produced as a single entity
2. Co-packaged: two or more separate products packaged together in a single package or as a unit
3. Cross-labeled: A drug, device, or biological product packaged separately 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.

The U.S. FDA has been developing and defining the appropriate pathways for combination products over the last 20 years. Drugs have been regulated since the beginning of the 20th century, but devices and biologics only began being regulated in the 1970s, and biologics did not receive their own center until the 1990s. The growth in the number of combination product submissions may have taken the agency by surprise, to some extent. The premise on which the FDA is built is that each type of product presents different safety and effectiveness questions. As a result, the products need to be reviewed by different experts organized into separate centers. Evaluation of combination products, on the other hand, requires the input of drug, biologic, and device experts who are currently employed in different centers. Consequently, the FDA must address both the regulatory questions regarding defining product types and appropriate applications and the logistical questions about how to facilitate efficient, effective reviews.

For creators of combination products, a lack of clarity by the agency has resulted in confusion and wasted resources. Manufacturers have historically had a difficult time identifying the primary mode of action for a product and, subsequently, the center to which an application should be submitted. Similarly, the number and type of applications or appropriate predicate (in the case of Premarket Notification) have been very difficult to discern. Once an application is under review, applicants often must respond to requests for the similar information from multiple centers that do not communicate with each other. The problems have resulted in much lost time and money and failed applications.

Draft Guidance

The *Principles of Premarket Pathways for Combination Products* draft guidance is the FDA's latest effort to stabilize the combination products pathway to market. The guidance is a response to the 21st Century Cures Act of 2016,[2] which introduced new requirements for the review of combination product applications. By and large, however, the draft guidance is repetitive of previous approaches. It briefly addresses the process for determining jurisdiction, including a Request for Designation. The majority of the document is a discussion of the types of applications available for each device-led, drug-led, and biologic-led product, although not much new information is provided. The exception is the annex, *Analysis of Pathway Availability for Device-Led Combination Products - Illustrative Examples*, which provides a detailed discussion of the types of predicates available for drug-device combinations using five hypothetical versions of an "externally-communicating device intended to be implanted in the abdominal cavity for drainage of excessive fluids" with antimicrobial

coating. The primary goal of the annex seems to be making it abundantly clear that 510(k) applications for combination products will not be able to rely on predicates of non-combination devices.

No Further Detail On Cross-Labeled Or Co-packaged Combination Products

With the lack of new information, industry's comments have centered on what is not in the document. Specifically, the draft guidance only addresses single entity products, providing no additional detail on cross-labeled or co-packaged combination products. As those products are the least explained in other guidance documents, industry is particularly frustrated. The problem is compounded by how the draft characterizes the number of applications permissible for a single product. The 21st Century Cures Act states that nothing in the statute should be deemed to prohibit a manufacturer from submitting two applications *unless* the agency deems it necessary. However, the new guidance states that "the Agency anticipates that a single application may not be appropriate in limited cases." That may be a relief for single entity manufacturers who would prefer to avoid duplicate submissions, but it is problematic for cross-labeled or co-packaged products with multiple manufacturers. A mandatory single application could present intellectual property concerns. Additionally, the draft does not address drug or device master files, another potential protection for intellectual property.

Devices As 510(k) Predicates

The point of most contention will certainly be the generalization that no combination product 510(k) submission will receive clearance if a stand-alone medical device is identified as a predicate. Commenters have been quick to point out that appropriateness of a predicate is a decision made on a case-by-case basis by product-center staff. They argue that some devices are effective predicates, such as coated wound dressings. It is unsurprising that this is the biggest sticking point. The 510(k) pathway is the most economical pathway to market. It is a poorly kept secret in the combination products world that any manufacturer looking to get a product to market with a device constituent part wants to submit a 510(k). However, there are a limited number of eligible predicate combination products available. Restricting applicants to those products alone shuts down that pathway for many, many manufacturers who would like to use it.

In Part 2 of this two-part article, we will examine the new EU draft guidance and how its approach differs from that of the FDA's.

References:

1. 21 CFR 3.2(e) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=3.2
2. https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act

About The Author:

Caitlin Bancroft, JD, is passionate about facilitating advancements in healthcare quality and medical technology by ensuring compliance for medical device, pharmaceutical, and biologic product regulatory requirements. Her experience in medical device regulation spans Class III, 510(k), PMA, De Novo, Modification, Reclassification, and IDE. Her work includes the review of FDA and EU regulations concerning quality management systems, cGMPs, clinical evidence/trials, complaint handling, risk management, and registration requirements for product classification and regulatory compliance of medical device, pharmaceutical, biotech, and human tissue/cell products. She works closely with clinical, quality management, and product and process development teams to accomplish cGMP audits and write clinical evaluation reports on behalf of Pharmatech clients.