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OVERCOMING CHALLENGES TO THE PATH TO COMBINATION PRODUCT DEVELOPMENT

Combination products have the potential to vastly improve medical care, making treatment more effective and safe, as well as improving compliance for patients. But because of the novelty and complexity of such products, companies face unique challenges in navigating them through regulatory channels and bringing them to market. To ensure timely and successful review, companies need to understand the current approaches to combination product regulation and develop strategies for partnering with the FDA during product development and approval. The following answers to commonly asked questions will help shed light on this challenging and exciting process.

Q: WHAT IS A COMBINATION PRODUCT?

A: According to the FDA, a combination product is one composed of two or more regulated components — any combination of a drug and device; biological product and device; drug and biological product; or drug, device, and biological product. The FDA's definition is quite inclusive, encompassing drug-coated devices, drugs packaged with delivery devices in medical kits, and drugs and devices packaged separately but intended to be used together.

Because combination products don't fit neatly into the traditional categories of drugs, medical devices, or biologics, the FDA is in the process of developing new procedures for reviewing their safety and effectiveness.

Q: HOW DOES THE FDA CATEGORIZE COMBINATION PRODUCTS?

A: To help determine the most appropriate regulatory pathway, the FDA developed a categorization scheme for combination products. Under this scheme, a product is placed into one of nine categories:

1. Convenience kit or co-package
2. Prefilled drug delivery device/system
3. Prefilled biologic delivery device/system
4. Device coated/impregnated/otherwise combined with drug
5. Device coated or otherwise combined with biologic
6. Drug/biologic combination
7. Separate products requiring mutually conforming labeling
8. Possible combination product based on mutually conforming labeling of separate products
9. Other type of combination product

Q: WHAT IS THE PMOA RULE AND HOW DOES IT AFFECT THE REGULATION OF A COMBINATION PRODUCT?

A: The PMOA — or Primary Mode of Action — regulation is the rule governing assignment of a new combination product to one of the three FDA regulatory centers for review: the Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), or the Center for Devices and Radiological Health (CDRH).

The FDA defines PMOA as "the single mode of action of a combination product that provides the most important therapeutic action of the combination product."

Products might have a drug, biologic, or device primary mode of action. For example, if the PMOA of a drug-device combination product is attributed to the device, it will be assigned to CDRH for premarket review. An example of such a product is a drug-eluting stent.

Q: WHAT HAPPENS WHEN PMOA ISN'T CLEAR?

A: The intent of the PMOA rule is to enable the FDA to make decisions based on assessment of the product as a whole and the determination of its intended use and effects. In cases where the primary mode of action is unclear, assignments are made based on previous designations for similar combination products and each center's relevant experience with the combination product components. Products will be assigned to the center with the most experience related to the most significant safety and effectiveness questions presented by the product.

To avoid surprises, the FDA recommends that companies discuss jurisdictional issues with the Office of Combination Products staff at an early stage in the development process. Browsing the FDA's Office of Combination Products (OCP) Website (fda.gov/oc/combination), which includes 140 examples of approved combination products, will provide a sense of how review processes have played out thus far.

According to OCP's Director Mark Kramer, in 75% of the cases, the agency agrees with the sponsor as to the PMOA of a product.

Q: WHAT IS AN RFD?

A: A Request for Designation (RFD) is the formal document submitted by the sponsors of a combination product providing information the FDA needs to determine the regulatory identity of a product as a drug, device, biologic, or combination product and assign the product to the appropriate center for review and regulation.

Q: WHAT IS THE PROCESS FOR SUBMITTING AN RFD FOR A COMBINATION PRODUCT?

A: When the jurisdiction of a combination product is unclear or in dispute, sponsors should submit a formal RFD to the Office of Combination Products. It is not necessary to submit an RFD for every combination product; only sponsors who are uncertain about the

proper designation of their product and appropriate regulatory pathway need to file such a request. The FDA advises that sponsors should do this before filing any application for premarket review and as soon as there is sufficient information for the agency to make a determination.

The RFD — to be no longer than 15 pages — should include:

- Description of the product, including classifications, identification of components, and chemical, physical, or biological composition;
- Results of developmental work;
- Description of manufacturing process;
- Proposed use, known modes of action, schedule of use; and
- Description of related products.

Full details and guidance for submitting an RFD are provided on the OCP Website (fda.gov/oc/combination/howtowrite.html).

Q: WHAT IS THE ROLE OF THE OFFICE OF COMBINATION PRODUCTS?

A: The OCP has overseen combination product regulation since December 2002. Its primary role is to ensure "timely and effective pre-market review," although actual reviews are done at one of the three FDA regulatory centers, based on the product's PMOA.

In its capacity as a facilitator, the OCP has taken an active role in reaching out to industry representatives and developing resources to streamline the regulatory process.

The OCP also maintains a combination products tracking database, enabling it to monitor how the review process is working and pinpoint any bottlenecks.

A study commissioned by the FDA, published in February 2006, found that manufacturers value the work of the OCP and its efforts to bring predictability, transparency, and consistency to the process of combination product review.

Q: HOW WILL MEDICARE REIMBURSEMENT FOR COMBINATION PRODUCTS DIFFER FROM REIMBURSEMENT FOR TRADITIONAL PRODUCTS?

A: If a combination product receives approval from the FDA, the sponsor may next choose to obtain national coverage and reimbursement from the Centers for Medicare and Medicaid Services (CMS). CMS will require evidence that the combination product will provide a clinically more effective therapy than is currently offered. In the case of a novel combination product, the lack of precedence for comparison makes coverage decisions challenging. CMS also wants companies to demonstrate that the combination product will provide a significant health benefit. A coverage decision process however, for combination products, has yet to be defined. CMS is not supposed to consider cost when making a national coverage decision, although there are recommendations for it to begin doing so.

Because CMS coverage will greatly influence physician adoption of the combination product, companies are advised to begin the reimbursement process as early as possible. This will help to decrease the lag time between FDA approval and CMS coverage, allowing the combination product to reach its target populations sooner.

Q: WHAT CHALLENGES WILL A SPONSOR ENCOUNTER IN MARKETING PRODUCTS IN THE EUROPEAN UNION?

A: For companies pursuing European markets, the standard challenges of international distribution are compounded by the challenges of regulation for combination products.

In general, companies wishing to market their products in Europe will have to go through an initial product designation phase and then review, as in the United States. Since there is no counterpart to the OCP in Europe — and no separate agency or set of regulations for combination products — companies will have to familiarize themselves with Europe's Medicinal Products Directive and Medical Devices Directive and determine for themselves which might apply to their product.

In addition to European regulatory requirements, there may be country-specific issues that need to be addressed.

Q: WHAT ARE REGULATORY BODIES AND THE INDUSTRY DOING TO ADVANCE THE FIELD OF COMBINATION PRODUCTS?

A: Industry professionals, academics, and representatives from other regulatory agencies continue to provide feedback to the OCP about the combination product regulatory process.

Several professional and trade organizations — including the Regulatory Affairs Professionals Society (RAPS), a professional society representing the regulatory affairs profession, and the Combination Products Coalition (CPC), a trade organization representing pharmaceutical, biologic, and medical device manufacturers — have been working with the OCP and advocating on behalf of industry concerns.

Creative, strategic approaches and open channels of communication between regulatory agencies and manufacturers are crucial to ensuring success in combination product development. Companies that help define the combination products market now, through participation in industry events and feedback on FDA guidance documents, will be well-positioned to lead the industry tomorrow.

Christine Ford is Event Director for PharmaMedDevice, a Reed Exhibition conference, which is scheduled for April 24-26, 2007, at the Jacob K. Javits Center, New York; U.K.-based Reed Exhibitions' portfolio of more than 460 shows includes the world's most respected trade and consumer events. For more information, visit pharmameddevice.com.

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