Blurred boundaries

The Office of Combination Products sorts out jurisdictions and opens up communication between FDA centers.

BY DAVID FILMORE

In medical product regulation, like law enforcement, determining jurisdiction is critical to avoiding confusion and inefficiency. But "border crossings" between drugs, biologics, and devices—categories that follow distinct regulatory paradigms—are making assigning regulatory authority for products more difficult.

A relatively new department in the FDA called the Office of Combination Products (OCP) is charged with handling this issue. Formed in December 2002 at the behest of the Medical Device User Fee and Modernization Act, OCP is the internal and external "go-to point" for resolving jurisdictional questions and facilitating consultations between historically disengaged FDA centers, says OCP director Mark Kramer.

The agency defines combination products as drug–biologic, drug–device, biologic–device, or drug–biologic–device permutations grouped either as single entities, in common packaging, or in separate packaging but labeled for combined use.

An example is Cordis's Cypher stent, the first drug (sirolimus)-eluting coronary stent. The up-and-coming technologies of tissue engineering and personalized medicine evoke combination product models as well.

According to Kramer, a request for designation (RFD) process for assigning combination or other potentially ambiguous products to the agency's drug, biologic, or device approval centers has been in place since 1991. However, he says, the industry has called for more clarity on the issue.

"Clearly," he admits, "there were examples of products that were in regulatory limbo for some time because we weren't quite sure how to handle them."

Even before the congressional mandate, Kramer says, the agency recognized that "the numbers and types of [combination products] were going to continue to grow."

A 2003 analysis of the combination products market by Front Line Strategic Consulting forecasted a $5.9 billion market in 2004 to increase to $9.5 billion by 2009.

This expansion, Kramer expects, will lead to increased regulatory challenges.

Today, he says, typical combination products have one constituent that is clearly subsidiary to the other, such as devices that supplement drugs with novel delivery mechanisms or drugs that support a device's activity (e.g., antibiotic-coated catheters). "But," he observes, "we are increasingly seeing products where two components are equal players, doing two completely different things."

A hypothetical example Kramer cites is a coronary stent that elutes an antiarrhythmic drug (instead of a tissue-growth blocker, which directly supports a stent's activity, as in the Cypher stent). Another example is a contact lens used for vision correction that elutes a glaucoma drug.

This new trend toward fully partnered combinations has regulatory implications, because it muddles the process of identifying a product's primary mode of action—the standard criterion for assigning jurisdiction. In May, OCP published a proposed rule (*www.fda.gov/OHRMS/DOCKETS/98fr/oc03366.pdf*) to formally define "primary mode of action" in federal regulations, and to delineate an algorithm that considers past experience with similar combinations and key safety and efficacy issues for cases when the primary constituent of a product isn't obvious. Under this approach, the contact lens/glaucoma treatment, for instance, would be assigned to the Center for Drug Evaluation and Research, as the drug has more significant safety and efficacy issues than do contact lenses.

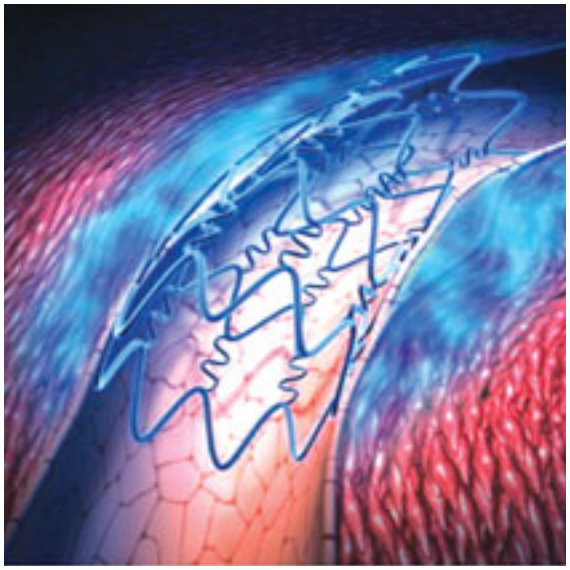
Such designations define the general regulatory scheme a product will need to follow, and they allow the agency to present a single face when dealing with a company. But this doesn't resolve the issue. Crucial expertise will often reside outside the primary review center. And, traditionally, Kramer explains, reviewers from one center have looked at another center as a "black box."

"The centers are differently organized," he says. "When one center works with another there might be somewhat of a strain."

OCP has implemented a standard operating procedure for intercenter consulting or collaborating—processes that have traditionally been associated with slow turnaround times, Kramer says. In addition, the office monitors these consultations, facilitates intercenter working groups, and provides staff training. Even in the postmarketing stage, OCP aids in the interactions for adverse event and GMP compliance monitoring.

"We are involved whenever one center requests help from another," Kramer says. The efforts have "gone a long way to systematize the whole process." ■

CORDIS CORP.



Tag-team medicine. The Cypher coronary stent holds open the artery and elutes sirolimus to prevent reclogging.