Combination products neglected by FDA device evaluation

In a damning evaluation of the US Food and Drug Administration's 510(k) program, which is used to clear medical devices similar to those approved previously, the US Institute of Medicine (IOM) issued a report on 29 July calling for a complete overhaul of the 35-year-old device regulation system. The IOM's conclusions harshly criticized the 510(k) process for clearing new devices on the basis of their similarity to existing products without evaluating safety and effectiveness data. But the 245-page report committed a mere two pages to what some consider an equally insidious problem affecting the approval of some kinds of medical devices: the review of combination products that straddle the divide between a device and a small-molecule- or biologic-based drug.

"We'd like to see the FDA be proactive in however it approaches combination and companion products," says IOM panel member Steven Gutman, a pathologist who directed the FDA's Office of *In Vitro* Diagnostic Device Evaluation and Safety for six years and now serves as associate director of the BlueCross and BlueShield Association's Technology Evaluation Center in Alexandria, Virginia. Although the report focused on pure devices, he concedes that "we don't think it would be inappropriate if the FDA stepped back and looked at the whole panoply of products it regulates."

Because small-molecule drugs, biologics and devices are all handled by separate centers at the FDA, combination products by definition fall under the domain of at least two distinct entities. But the FDA hierarchy forces developers to shuttle their products through just one center, with the overseeing center determined by the product's primary mode of action. This process is flawed, experts say, because a single center does not have the broad expertise to effectively evaluate the safety and efficacy of a combination product.

A former FDA official who oversaw combination product regulation and requested anonymity says that many developers push to have their combination products evaluated by the FDA's Center for Devices and Radiological Health since the device center, as pointed out by the IOM report, often sets a lower bar for approval than the Center for Drug Evaluation and Research or the biologics equivalent. "It puts the agency in a really difficult place," the ex-employee said.

This variability in regulation and ultimate approval presents an opportunity for sponsors to game the system. "There's an incentive for sponsors of new products to be very strategic in how they portray their products to ensure primary review by one center or another," says Jason Sapsin, a former FDA attorney now at the Polsinelli Shughart law firm in Denver.

"Understandably, they want to make sure their products go through the processes that they understand the best."

The problem has not gone unnoticed by the FDA. In response to mounting applications for combination products and their increasing complexity, the government created the Office for Combination Products (OCP) in 2002 to help sponsors choose the proper center for their product.

But the OCP is just a start, says Michael Drues, president of Vascular Sciences, a consulting group based in Grafton, Massachusetts. He had hoped that the office would transition into a center in charge of all combination product regulation. But, instead of revamping the system, "we need a new regulatory model that will continue to encourage companies to develop these life-saving products," he says.

For now, the three-center model seems to be working with OCP "satisfactorily," according to Jeffrey Shapiro, a healthcare lawyer focusing on medical device law at Hyman, Phelps and McNamara in Washington, DC. However, the number of new applications for combination products increased from 249 in 2004 to 377 in 2009. As these products become more common, "it is possible that the FDA may want to rethink how they organize their resources to approve [combination] products," he says.

Hannah Waters

FDA reorganization inspires hope for better coordination

In an agency-wide e-mail message on 13 July, US Food and Drug Administration Commissioner Margaret Hamburg unveiled a massive reorganization of the regulatory watchdog's 41-year-old management structure. "The most obvious change you will see," she wrote, "is that the Agency's programs, in terms of a reporting chain to me, will be divided into 'directorates' that reflect the core functions and responsibilities of the Agency." In addition to the existing offices, she said the FDA would also create a new Office of Operations as well as a deputy commissioner for Global Regulatory Operations and Policy "focused on grappling with the truly global nature of today's world."

For the pharmaceutical industry, the most important change could be the addition of the Office of Medical Products and Tobacco, which will be directed by Stephen Spielberg, who will assume the new post by the end of September. Spielberg is tasked with helping to coordinate work across the FDA's centers for drug, biologics, medical devices and tobacco products. In the

past, each of these centers reported directly to the commissioner.

Adding this extra layer of management should help the agency to better coordinate interactions between its centers. This might help, for example, a pharmaceutical company seeking approval of a new cancer drug (which undergoes review at the FDA's Center for Drug Evaluation and Research) and a so-called 'companion' diagnostic test to see who would benefit from the medication (which is reviewed by the agency's Center for Devices and Radiological Health). Spielberg will also watch over the Office of Special Medical Programs, which, among other things, oversees the regulation of orphan drugs.

Spielberg has had executive-level experience working in industry for the drug giants Merck and Johnson & Johnson. Most recently, however, he has served as the director of the Center for Personalized Medicine and Therapeutic Innovation at Children's Mercy Hospital in Kansas City, Missouri.

Analysts have hope that his previous posts will enable him to accelerate the approval process. "Spielberg can be the bridge that helps actualize agency regulations to facilitate the translation of breakthrough science into novel therapies," says Bernard Munos, founder of the InnoThink Center for Research in Biomedical Innovation in Indianapolis, Indiana and a former strategic advisor at Eli Lilly.

There is hope that Spielberg will have time to take on particularly high-profile issues in drug regulation that the FDA has yet to fully address. For instance, Sophia Snyder, a pharmaceutical analyst at IBISWorld in Santa Monica, California, says she expects Spielberg to work on defining a regulatory pathway for follow-on biologics. Although the FDA has not published final guidelines for approving such generic versions of biologic drugs, Snyder calls them a "worthwhile investment for brand-name pharmaceutical companies," because, for example, they should command a high price.

Mike May