Denise Myshko

Advancing Innovation *with* Better Regulatory Science

The FDA is in the middle of an effort to improve regulatory science and how new medicines are approved.

The Food and Drug Administration is in the midst of a huge undertaking to transform the way medical products are developed, evaluated, and manufactured. And while much progress has been made, there is still work to be done to improve the regulation of drugs and medical devices.

FDA officials recognize the need to find effective ways to help speed the availability of promising new products, and they are working to achieve an appropriate balance between benefits and risks by offering a range of development pathways depending on the product and the disease being treated.

Last year's FDA Safety and Innovation Act — FDASIA — created a new expedited approval pathway for breakthrough therapies, designed for when preliminary clinical data suggest that a new drug holds real promise to offer substantial improvements over available therapies to treat a serious condition.

The key to further success is continued innovative approaches to streamline and optimize the drug development process, says Steve Hamburger, Ph.D., senior director for regulatory affairs at Millennium: The Takeda Oncology Company.

"Some important areas of continued regulatory science focus that will be beneficial to the delivery of new treatments to patients are increased novel personalized medicine efforts, wider use of different statistical approaches, changes in approaches to accept manufacturing and drug analysis as well as earlier meetings and communications between FDA and sponsors," Dr. Hamburger says.

In addition, Dr. Hamburger believes enhancement of the information technology infrastructure may improve the regulatory process by rapid analysis of large, complex nonclinical, and clinical data sets early in the drug development process, potentially improving the ratio of benefit to risk and targeting drugs to the right patients, irrespective of the specific disease.

Industry experts agree there is a need for transparency and increased communications between regulators and sponsors.

Pharmaceutical companies such as Eli Lilly & Co. look for a regulatory process that is predictable in its judgments, decisions, and criteria on which those decisions are based and that is scientifically strong and is transparent, says Rob Metcalf, Ph.D., head of regulatory affairs, at Lilly.

"We believe that the FDA, through PDUFA V and implementation of the new NME review model, continues to advance a number of these principles," he says. "As an industry, we've given up a couple of months in the new model for review of new NMEs and new biologics but we believe strongly that the commitments that the FDA has made to engage with sponsors throughout this process will enhance a number of the principles around science- and judgment-based decisions, as well as the predictability and transparency of the process."

He says key to the confidence of the public is good transparency on the decision-making process and on the basis on which those decisions are made.

"The FDA continues to make advances in terms of the transparency in not only what the decision is but the basis that it makes that decision on," he says.

Coleen Klasmeier, partner and head of FDA practices, of the law firm Sidley Austin, says what's often missing in regulatory communication is a candid conversation with industry about the practical ways in which the regulatory science initiative affects the basic question at the heart of what the FDA does, which is how does it know when a medicine is effective.

"What is needed is a much more fundamental and profound conversation about how to establish that something is true," she says.

Dr. Metcalf says there have been a number of positive changes at the agency.

"The agency is building its regulatory science capability, and we believe these changes will result in a number of improvements being enabled through the completion of PDUFA V last year," he says. "The FDA is committed to a number of regulatory scientific goals and objectives around the qualification of biomarkers and pharmacogenomics; the use of patient reported outcomes; getting patient input into regulatory science; benefit risk; as well as establishing strong benefit-risk frameworks, meta analyses, and how the agency approaches rare diseases."

But he says there is a need for continuous collaboration between the FDA and the industry as well as with other stakeholders in healthcare.

"We are dealing with a system that is inherently very complex; there is valuable expertise out there, not just within FDA and not just within pharma, but in academia as well as in the medical and patient communities," Dr. Metcalf says. "The solutions we are looking to deliver to address significant unmet medical need are not trivial and, therefore, the more stakeholders we can bring together, the better off we will be in advancing meaningful healthcare solutions for patients. As much as we can encourage an environment of openness and collaboration by the FDA with the industry and others, I think we will continue to be a world leader in advancing medical innovation."

In terms of technology, KR Karu, pharmaceutical industry solution director, at Sparta Systems, says the agency is moving in the right direction.

"Regulators are keeping their eyes on technologies that aren't fully available yet to make sure they are staying on top of advancements," he says. "Personalized medicine is one such area. Regulators are taking a futurist view and are talking about how to regulate and facilitate these advances."

He says another example is the concept of quality by design.

"This is a major part of the third step of the initiative, which supports the new approach to improve product manufacturing and quality," Mr. Karu says. "Companies are now building quality into the design of manufacturing products instead of testing at the end. But that doesn't mean that batch testing has gone away."

Efforts to Improve Regulatory Science

Regulatory officials say to fully translate today's sophisticated scientific discoveries they require advancements in regulatory science — the knowledge and tools needed to assess and evaluate a product's safety, efficacy, quality, purity, and performance.

FDA Commissioner Margaret Hamburg, M.D., spoke about regulatory science at the MassBio meeting in March, saying the agency's approach involves the development of new methods, standards, and models it can use to speed the development, review, approval, and ongoing oversight of medical products.

The 2010 initiative set a lot of broad goals for the FDA for improving the science of what it does, says Chad Landmon, co-chair IP practice, chair of FDA practice group, at the law firm of Axinn, Veltrop & Harkrider.

"In particular, the agency focused on working with resources outside of the FDA, for example, the Reagan-Udall foundation, academia, and others to improve the work at the agency," he says.

Mr. Landmon says the FDA is overburdened and takes too long to reach decisions.

"Obviously, regulators want to be careful and they want to get the decision right," he says. "But it shouldn't take the FDA years to come to a conclusion. The agency needs to bring in more resources from the outside to get to decisions faster."

Dr. Hamburger expresses the need for continued efforts in the identification and prediction of adverse responses and drug-drug interactions, greater acceptance of biomarkers for safety and efficacy efforts, acceptance of novel methods and approaches to improve manufacturing and analytical methods, and tools to enhance the rapid review of dossiers at all phases. PV

FDA's Regulatory Science Initiative

Regulatory science is the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

In February 2010, the FDA launched its Advancing Regulatory Science Initiative (ARS), building on the achievements of existing agency programs, such as the Critical Path Initiative's groundbreaking efforts to transform the way medical products are developed, evaluated, and manufactured.

The agency's strategic plan, released in August 2011, identifies several priority areas of regulatory science where new or enhanced engagement is essential to the continued success of FDA's public health and regulatory mission. The priority areas are:

- **Modernize toxicology** to enhance product safety
- **Stimulate innovation** in clinical evaluations and personalized medicine to improve product development and patient outcomes
- **Support new approaches** to improve product manufacturing and quality
- **Ensure FDA readiness** to evaluate innovative emerging technologies
- **Harness diverse data** through information sciences to improve health outcomes
- **Strengthen social and behavioral science** to help consumers and professionals make informed decisions about regulated products

The agency has established three Centers of Excellence in Regulatory Science — one in Arkansas, one at Georgetown University, and one at the University of Maryland. These centers are conducting targeted research, strengthening education and training in regulatory science, and bolstering scientific exchanges and collaboration.

The agency is also working with the Reagan-Udall Foundation, a private and independent nonprofit research organization that was created by Congress in the FDA Amendments Act of 2007 to advance the mission of the FDA to modernize medical, veterinary, food, food ingredient, and cosmetic product development, accelerate innovation, and enhance product safety.

In November 2012, the FDA started a campaign intended to promote regulatory science to the public by explaining the field in plain terms. The agency also is working with stakeholders to advance the various fields of regulatory science.

In December 2012, the agency announced it would partner with LifeScience Alley to ensure that the United States maintains its status as the leader in regulatory science.

In January 2013, the FDA issued a grant proposal calling for groups to help it address a number of regulatory science issues, including those related to the communication of risk.

Source: Food & Drug Administration