The Changing Landscape of the FDA

An in-depth look at the FDA review and approval process and its impact on eye care providers.

The Food and Drug Administration (FDA) is a vision of two worlds: the focus of major regulatory reform that aims to hasten the approval process for high-quality drugs and devices, but also a federal agency significantly understaffed and bogged down in bureaucratic uncertainty.

The FDA has taken steps in recent years to improve its review and evaluation of drugs and devices, recently becoming more efficient, for instance, than the European Medicines Agency (EMA), its counterpart agency in Europe.[1] FDA officials also say they are now working closer than ever with private industry to develop product innovations and move products quicker to market.

Yet there is uncertainty ahead, as President Donald Trump seeks to "streamline the FDA" while pushing for even quicker product reviews. At the same time, Mr. Trump has called for a $40 million reduction in the agency's budget and proposes to double the amount the FDA receives in user fees, which may cause consternation among some drug and device makers. In addition, a slew of other changes—including a temporary hiring freeze, a new FDA commissioner, Mr. Trump's orders to reduce regulations, and the agency's sluggish review of generic drug applications—pose significant challenges to meeting the goal of increased efficiency in product approvals.

IMPACT ON OPHTHALMOLOGY

Through the political maelstrom and bureaucratic twists and turns, there is progress, according to Carl Tubbs, MD, an ophthalmologist with InSight Vision Group in Denver, a member of the American Glaucoma Society and president of the American National Standards Institute.

"We have seen a willingness from the FDA to move standard development forward in a more direct path," he says. "The process has included the presence of more consistently involved FDA members in the standards process so that our team is more familiar with ongoing issues and we do not need to readdress them, and what I perceive is better inter-departmental communication within the FDA itself."

The FDA's effort is reflected in the FDA's Center for Devices and Radiological Health's strategic priorities that "strengthen the clinical enterprise" program, says CDRH Director Malvina Eydelman, MD. Those strengths have been reflected in more efficiency within the agency, she says.

In 2011, it took the FDA to make what is known as an investigation device exemption (IDE) decision a median of 442 days. During 2015, the median number of days for full IDE approval was decreased to 30 days. Such IDE exemptions allow a device to be used to collect clinical data for premarket approval or premarket notification submission to the FDA. This year, the FDA's Center for Drug Evaluation and Research reported it exceeded most goal dates by 95% of novel drugs approved.

"We expect this trend to continue," Dr. Eydelman says.

Michael X. Repka, MD, medical director of government affairs for the American Academy of Ophthalmology, agrees: "It does seem that things are moving faster through the agency, on both the device and pharmaceutical side. It is never as fast as practitioners and innovators would like, but it has not slowed down to a crawl."

Last year, the FDA issued several guidances that significantly impact the ophthalmology industry, including the FDA's premarket studies of MIGS devices that "recommends nonclinical and clinical studies to support FDA approval of MIGS devices, says Dr. Eydelman.

The FDA also released draft guidance on its proposals for repackaging biologic products such as Avastin (bevacizumab; Genentech), a drug injected into the eye to slow vision loss in people who have wet age-related macular degeneration.

The agency's overall drug approval numbers are not all in the FDA's favor. In 2016, the FDA's Center for Drug Evaluation and Research approved 22 novel generic drugs, lower than the 54 novel drugs that were approved the year before, and below the average of 29 drug approvals per year on average during the past 10 years. According to Robert Pollock, a former acting deputy director of the FDA's Office of Generic Drugs, the agency has struggled to keep pace with generic applications, as well as meeting Generic Drug User Fee Amendment deadlines.

WORKLOAD WOES AND HIRING FREEZE

The feeling of being overworked and understaffed by FDA employees could be attributed, in part, to the quality of the applications as well as the FDA's undermanned staff: the agency estimates it needs to fill about 700 to 900 positions. The agency's effort to begin filling those positions was dealt a blow on Jan. 23 when Mr. Trump signed a presidential memorandum freezing government hiring.

That freeze was at least partially lifted in mid-April, but the impact remains uncertain. In a memo to FDA employees, Director of the Office of Management and Budget Mick Mulvaney wrote that he expected to assess positions in all federal agencies once they become vacant, and decide whether to fill them or to submit an overall work force reduction plan by September.

Dr. Tubbs says there are definite impacts from the hiring freeze and other administration moves. The freeze "reduces staff available to revise and work on our American National Standards Institute standards, as well as causes issues with travel restrictions for meetings," says Dr. Tubbs. "I understand that there are openings for FDA staff that cannot currently be filled, due to the hiring freeze. The natural conclusion is the creation of potential delays in the approval of new devices and medications, as well as other FDA duties. It is unclear that regulatory review 'overall' would be possible in the face of funding reductions."

TRUMP TARGETS BUREAUCRACY AT FDA

In a speech before a joint session of Congress in March, Mr. Trump complained about the "slow and burdensome approval process at the FDA." In his budget proposal, meanwhile, Mr. Trump called for a $40 million cut in FDA appropriations for the rest of fiscal 2017, with the focus on reduced staffing—of an agency many believe is already drastically shorthanded.

The White House's budget plan also seeks to "recalibrate" or collect FDA medical product user fees that would amount to $2 billion in 2018, double the amount collected in 2017. That would be a dramatic change from 2016 to 2017, during which user fees had decreased. The FDA has been charging companies user fees to review their products since 1992.

In 2016, the FDA approved 91 innovative devices, the highest number of any year since the user fee program began in 2003, Jeff Shuren, director of the FDA's Center for Devices and Radiological Health, told a Congressional subcommittee, referring to Medical Device User Fee Amendments.

The FDA has shown to be more efficient in its regulatory program than the EMA, according to a study published in the *New England Journal of Medicine* in April, that focused on therapeutic agents approved between 2011 and 2015. The study was authored by Nicholas S. Downing, MD, of Brigham and Women's Hospital, Audrey D. Zhang, AB, of the New York University School of Medicine, and Joseph S. Ross, MD, MHS, of Yale School of Medicine.

Among the 142 therapeutic agents that were approved by both the FDA and the EMA, the median total review time was 303 days through the FDA compared with 369 days through the EMA. For new therapeutic agents that were approved between 2011 and 2015, the regulatory reviews by the FDA were, on average, 60 days shorter than those by the EMA.

The speed of the regulatory review process will come under more intense scrutiny, but the FDA "continues to complete regulatory reviews more quickly than the EMA and has the potential to inform discussions regarding the reauthorization of the Prescription Drug User Fee Act (PDUFA)," wrote the study authors.

Mr. Trump's user fee hike proposal came after Congress concluded reauthorization hearings on user fee negotiations for the continuation of the PDUFA. Many suspect that Congress may tinker with the plans before the reauthorization of the PDUFA before it expires in October 2017.

INDUSTRY PUSHBACK

The Trump plan is not sitting well with all device makers or watchdog groups, especially since device and drug makers already reached tentative pricing agreements with Congress.

"Beyond the proposed increase in user fees being neither wise nor realistic, there is a dynamic being created that potentially puts hundreds of millions of dollars of FDA's budget authority appropriations at risk," the Alliance for a Stronger FDA, a not-for-profit consumer, patient, and research advocacy organization, said in a statement.

When asked about it, Scott Whitaker, president and CEO of the trade group Advanced Medical Technology Association, also known as AdvaMed, issued a statement: "With respect to the Medical Device User Fee program, we remain committed to the medical device user fee agreement as negotiated, which represents a substantial increase over current fee levels and will help speed new medical technologies to patients in need."

REGULATION CUTBACKS

In the meantime, other restrictions were proposed by the Trump administration, including an executive order that would require government agencies to phase out two regulations for every new one, under a plan to help small businesses by reducing regulatory costs. That plan, coupled with the hiring freeze, could wreak havoc in processing issues for the FDA, says Mr. Pollock.

Before the hiring freeze, the agency issued at least 100 guidances, which are meant to provide advice for industry on submission of quality applications, as a way of hastening the process. However, Mr. Pollock says this felt "like a tsunami," to many of those affected.

Some say the Trump Administration changes could also result in confusion: "How do you eliminate two regulations if you are putting out a new one?" Mr. Pollock asks. "How do you make that cut? If guidances are withdrawn, the FDA's effort to reduce drug prices could be thwarted if you cannot get generic drugs onto the market."

Jeffrey J. Kimbell, president of Jeffrey J. Kimbell & Associates, a life sciences lobbying group and former first executive director of the Medical Device Manufacturers Association, had a different take on the situation: "The FDA remains the gold standard, and the future is bright here, and with the anticipation of a smoother process, the industry is trying to get products to market and the FDA is trying to help people."

While the agency's top officials "have been really good, and have been aggressive in hiring people from the private sector to bring more firepower and expertise to the agency, with the hiring freeze in place, some of these people who were difficult to get to begin with may not join the agency, so this is a problem," Mr. Kimbell says.

The hiring freeze also could have an impact on the FDA's ability to implement the 21st Century Cures Act, a law enacted under the Obama Administration designed to improve approvals of drugs and devices. The law provides $6.3 billion to accelerate the "discovery, development and delivery of new cures and treatments," with a move toward spurring development of new drugs and medical devices.

WHAT HAPPENS NEXT?

In a statement, Andrea P. Thau, OD, president of the American Optometric Association, applauds the legislation for "speedier drug and device approvals." She said the association wants to play an "active role in the implementation of 21st Century Cures to ensure that decision makers are armed with a clear science and evidence-based understanding of benefits and risks."

Some groups, such as Public Citizen, the Washington, D.C.-based advocacy group, have decried the legislation, calling it too favorable to the pharmaceutical and medicine device industry and eroding standards for the FDA.

Former FDA commissioner Robert M. Califf, MD, MACC, issued a recent warning about the need for strength in hiring: "Quite simply, we cannot accomplish our mission and deliver on the promise of science, with data-driven results and rigorous research and analysis without sustaining, solidifying and strengthening our talented work force."

Dr. Califf resigned from his post on Jan. 20. In April, Mr. Trump chose Scott Gottlieb, MD, a former deputy FDA Commissioner who served from 2005 to 2007, as the new FDA Commissioner. Dr. Gottlieb was confirmed by the Senate on May 9 by a vote of 57 to 42. Dr. Gottlieb has supported deregulating medical products and has said the FDA is too slow in its approval process, consistent with Mr. Trump's positions.

Although some questioned Mr. Trump's naming of Dr. Gottlieb to head the FDA, citing the nominee's reported close ties to the pharmaceutical industry, Mr. Kimbell described him as a terrific choice to lead the agency.

"I am not sure there is a more qualified person in the country to be the commissioner of the FDA. He is an administrator, an entrepreneur, a practicing physician (internist), a cancer survivor (from Hodgkins' lymphoma), and knows Washington having been at the FDA and Centers for Medicare and Medicaid Services in the Bush Administration," Mr. Kimbell says. ■

1. Downing NS, Zhang AD, Ross JS. Regulatory review of new therapeutic agents—FDA versus EMA, 2011-2015. *N Engl J Med.* 2017; 376:1386-1387.