Denise Myshko

Beyond User *Fees*

A new law could help provide increased communication and transparency with U.S. regulatory authorities.

The Food and Drug Administration Safety and Innovation Act (FDASIA) — a new law that went into effect in October 2012 — is expected to bring overarching changes to the review of new medications. The law includes the reauthorization of the Prescription Drug User Fee Act (PDUFA V), Medical Device User Fee Act (MDUFA III), and new provisions and user fees for biosimilars and generic products.

But experts say other provisions in the law are expected to have more far-reaching effects that are mostly positive for the industry. In fact, experts say the changes in the law could help to create a more proactive and transparent regulatory review process, with enhanced communication between sponsors and regulators, enhanced supply chain oversight, a more structured approach to risk/benefit analysis, and regular domestic and foreign inspections.

Any regulation or guidance that provides additional transparency and clarity and opportunity for dialogue is good for the industry, says Lisa Jenkins, Ph.D., director, strategic regulatory services, at CSC Life Sciences.

"FDASIA's big focus is transparency and additional control, particularly in foreign inspections and enforcement capability," Dr. Jenkins says. "Regulators are going further with transparency about API and finished product manufacturers. But there are so many changes beyond CMC with the reauthorization that I believe there will be a radical shift in the way that regulatory business will be done. But I also see this as being incredibly positive if companies take advantage of it."

There are aspects of regulatory science that are supported in the new law that are very important, says Jay Siegel, M.D., chief biotechnology officer, and head, global regulatory affairs, at Janssen Research & Development LLC, Janssen Pharmaceutical Companies of Johnson & Johnson.

"Regulators are going to have access to more expertise on rare diseases, more resources to focus on important areas such as meta analyses and biomarkers, and improved opportunities to learn and share best practices across their divisions," he says. "They're going to invest more in Sentinel, which is part of the effort to use electronic health records and other electronic databases. This is critically important because better postmarketing safety assessment will protect and inform patients and will make regulators and developers more comfortable about approving and marketing drugs."

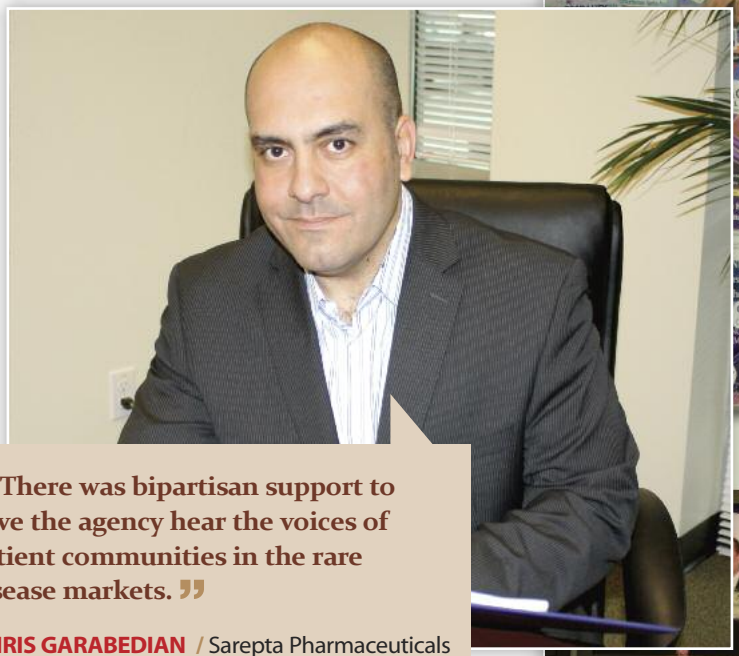
Terry Hisey, vice chairman and U.S. life-sciences leader for Deloitte LLP, says overall the new legislation will be positive.

"It will be positive for the innovator companies, it will be positive for the regulators in the execution of their responsibility, and it will be positive for patients because it's going to provide the resources and create the path by which more quality therapies will find their way to market," he says.

The new law provides a great opportunity for small biotech companies that are focusing on rare diseases, says Chris Garabedian, CEO of Sarepta Pharmaceuticals.

"It's clear from the legislation that the FDA should try to use the accelerated approval pathway for these products more often," he says. "Historically, the accelerated path has been used for oncology and HIV products. There was bipartisan support to get this passed as part of the PDUFA V legislation; it sends a signal to the FDA and to the industry to hear the voices of patient communities and patients who live with rare diseases. These diseases often carry a risk-benefit ratio that requires more flexibility by the FDA to approve drugs based on early signals of efficacy or surrogate markers."

David Fox, partner at Hogan Lovell's life-sciences practice, says there is more support



> **“There was bipartisan support to have the agency hear the voices of patient communities in the rare disease markets.”**
>
> **CHRIS GARABEDIAN** / Sarepta Pharmaceuticals

> **“There is an expectation that additional time in the review cycle will improve the process in terms of both timeliness and the quality of issue resolution.”**
>
> **DR. JAY SIEGEL** / Janssen Research & Development

both in the law and within the culture of the regulatory agency for innovative therapies, highly targeted therapies, and niche products.

“There is now a new program for breakthrough medications that will allow the agency to push through approval to fill an unmet need,” he says. “We’ve also crossed into new and productive territory in terms of personalized medicine and marrying drugs and biologics with diagnostics to get targeted therapies. There will be continued exploration of biomarkers for very serious disease conditions as targets for demonstrating efficacy, and PDUFA encourages greater use of biomarkers.”

New User Fees

The new law reauthorizes PDUFA and MDUFA and provides for new user fees for biosimilars and generic products. Experts say this will change development, approval, and postmarketing activities for these products.

Funding for the agency from 2013 through 2017 is expected to increase $3.2 billion compared with 2007 to 2012, according to the Congressional Budget Office. More than half of the money comes from new user fees on generic drugs and biosimilars.

FDASIA is going to lead to greater transparency, a higher quality of applications, and more first-round approvals, Dr. Jenkins says.

“From an FDA perspective, the new user fee requirement will enable regulators to communicate with the industry more effectively, be able to tell sponsors what it is they require, and enable a better quality review,” Dr. Jenkins says. “No one likes fees; but they will give the agency the resources to talk more with sponsors, provide updated guidances and opinions on important regulatory topics, and ultimately, that will translate into industry knowing what the standards are. Reviews are going to be a lot more predictable, and there will be more opportunity to reach out to the FDA to get answers in a timely fashion.”

In the generics area, there is a backlog of applications, and the FDA is charging a backlog fee for any application that was still under review and not approved as of October 1, 2012.

Mr. Fox says the move to collect user fees from generic drug applicants was debated for a long time.

“There was a tipping point when it became clear that the application backlog could not be worked down without a significant infusion of resources,” he says. “While the generic drug industry was concerned about the cost because their margins are thinner than on the branded

Analysis of FDA Review Times

An analysis done by Dr. Jay Siegel and his colleagues, Andrea Masciale and Patricia DeSantis, at Janssen Research & Development LLC, evaluated review times from submission to approval. Data show that times to approval were longer under the PDUFA IV approved submission cohort (i.e., applications submitted in fiscal year 2008 or 2009 and approved within two years) than for the PDUFA III approval submission cohort (submitted 2003-2006 and approved within two years). This trend was most apparent for priority applications, but also for standard applications.

In contrast with the PDUFA III cohort, only a minority of applications in the PDUFA IV cohort was approved by the original first cycle goals established in PDUFA; most applications required cycle extensions or second cycles to allow resolution of issues identified by the FDA during review. Median and mean times to approval were well in excess of the original PDUFA review goal.

Dr. Siegel and his colleagues suggest that length of time to the first cycle review deadline is a less important driver of the time to approval than the frequency of cycle extensions and second cycles. Process enhancements that expedite identification, communication, and resolution of issues might decrease the numbers of extensions and extra cycles, shortening time to approval.

Some experts at the FDA and in industry have hypothesized that the added responsibilities in FDAAA — specifically, the need to hold more AC meetings and the advent of REMS — could be major drivers of the lengthening application approval times observed early in the PDUFA IV process. The Janssen study supported this argument in that the presence of an REMS and/or an AC meeting for an application was associated with a substantially longer time to approval and a substantially lower likelihood of approval by the original PDUFA goal date.

Source: Dr. Jay Siegel, Janssen Research & Development LLC

> "The next great breakthrough will be when the law catches up with the industry when it comes to combination products."
>
> **DAVID FOX** / Hogan Lovell

> "Congress recognized there are unmet medical needs and provided new approval mechanisms to speed drug development and approval and extended the accelerated approval path to rare diseases."
>
> **DIANE BERRY** / Sarepta Pharmaceuticals

Regulatory Changes

The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012, gave the FDA the authority to collect user fees from the industry to fund reviews of innovator drugs, medical devices, generic drugs, and biosimilar biologics. It also reauthorized two programs that encourage pediatric drug development.

Changes include:

- **Generics applications:** Any original ANDA that has not been withdrawn, tentatively approved, or approved by Sept. 28, 2012, is considered pending and is subject to a backlog fee.
- **Biosimilar fees:** This adopts the format and structure for prescription drug user fees. A significant difference is that it also includes development program fees that apply to investigational biosimilars. In addition, an annual fee will be assessed for each year following the initial fee.
- **Review times:** FDA will get an additional 60 days for the review of NDA/BLAs applications. The goal for the additional review time allows for increased communications to reduce the number of review cycles necessary to get to approval.
- **Pediatric drugs and devices:** The law makes permanent the Best Pharmaceutical for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Until now, BPCA and PREA have been subject to reauthorization every five years as part of the PDUFA process.
- **Antibiotic incentives:** Incentives to encourage companies to develop new antibacterial and antifungal drugs intended to treat serious and life-threatening infections, such as MRSA. The incentives include: five-year extensions of exclusivity otherwise available to new drugs under the Hatch-Waxman and Orphan Drug Acts; Priority Review; and Fast Track status.
- **Breakthrough therapies:** The law creates a process to speed the review for some rare diseases. It also establishes a priority review voucher program for rare pediatric diseases. The FDA is in the process of developing guidance related to this.
- **Increased patient participation:** The new law will assist the agency in developing and implementing strategies to solicit the views of patients during the medical product development process and consider their perspectives during regulatory discussions.
- **Drug shortages:** The FDA has new authority to combat shortages of drug products in the United States and impose new requirements on manufacturers regarding early notification to the FDA of issues that could lead to a potential shortage or disruption in supply of a product.

side, they chose cost to improve timeliness of approvals."

Mr. Fox says the overall goal now is to work down the backlog by 2017. He says another consideration was that the exclusivity that a generic earned for being the first with a submitted application was being put in jeopardy by the longer review times.

"Review times have gradually gone up over the last decade," he says. "Back-of-the-envelope estimates of median review times show that they have gone from 14 months to 18 months to 18 months to 24 months and then 24 months to 30 months. The law up until July 2012 was that if the generic could not be tentatively approved and go through one substantial review within 30 months, it would forfeit its exclusivity. Congress approved a patch that extends that period to 48 months, which will come back to 42 months, and then down again to 30 months as the backlog is reduced."

For biosimilar products, the agency is creating a structure that is very similar to the small-molecule side, Dr. Jenkins says.

"But regulators want to avoid some of the issues that the prescription drug office is seeing as they are flooded with applications," she says. "They are putting a structure in place with the anticipation that regulators are going to become busy very quickly. For biosimilars, there is an initial fee, similar to an application fee and there is an annual fee. There is no other group within the FDA that currently has an annual fee. I would not be surprised if this fee structure permeates into other areas (for example, prescription drugs)."

Biosimilars are expected to be a huge part of the global biopharmaceuticals market by 2020, predicts a new report from GBI Research. In the United States, the biosimilars market could be valued at $9 billion by the end of the decade, despite the fact that the first ones will only enter the market in 2014.

New Processes

Industry experts say FDASIA and PDUFA V will enable enhanced scientific communications with sponsors during drug development and throughout the drug review process. Under the new law, the FDA will have increased resources and staffing to validate the use of new scientific tools, such as pharmacogenomics and biomarkers, which can help demonstrate therapeutic benefits more rapidly. The agency also will have dedicated resources to evaluate the use of meta-analyses and provide guidance on standardized methodologies for their use in drug review and safety monitoring.

To promote greater transparency and improve communication between the FDA review team and the sponsor, the FDA will establish a review model that will apply to all

new molecular entity new drug applications (NME NDAs) and original biologics license applications (BLAs). FDA officials say the goal of the program is to improve the efficiency and effectiveness of the first cycle review process and decrease the number of review cycles necessary for approval.

FDA's current goal is to review and act upon 90% of priority review applications within six months, and 90% of standard review applications within 10 months. The new law adds two months to the beginning of the review cycle of new NDAs and BLAs to allow for initial review of the application and communication with the sponsor.

"There is a broad expectation that this additional time in the review process will likely improve the process in terms of both timeliness and quality of issue resolution," Dr. Siegel says.

Dr. Siegel and his colleagues at Janssen conducted an analysis of approval times under PDUFA IV and found actual time of the first cycle was not the key driver of approval time.

"Only 30% of priority applications were approved at six months," he says. "Of those that were approved within two years, 30% were approved within six months and 70% were approved between six months and two years. Similarly, only 42% of the standard applications were approved by 10 months in 2008 and 2009. In fact, the median time for approvals for products with a six-month cycle was more than 11 months and for the standard, which would have a 10-month cycle, was longer than 14 months."

Dr. Siegel says new processes that had been put in place by FDAAA were contributing to the complexity of the review process.

"Regulators were convening more advisory committee meetings," he says. "They are often held late in the cycle and they sometimes raise new issues or concerns that need to be addressed. There may be REMS and risk management programs that take some significant time to assess and then negotiate and develop. In addition, there are more global inspections, which create the need for state department approval and international travel."

"Our analyses showed that it was, in fact, applications that required advisory committee or REMS that were taking longer," Dr. Siegel says.

Mr. Hisey says by allowing more time for communication, there is a better chance the result will be a more comprehensive review that includes the right questions and considerations that can lead to an approved product sooner than would happen without the dialogue.

But Mr. Garabedian says he believes the additional review wasn't necessary.

"Part of the original idea around user fees was that the industry would pay to help staff up the agency to get the work done," he says. "The FDA is getting financial support from the industry to keep to timelines and six months seems reasonable for a priority review filing."

> "There are so many changes with the reauthorization that I believe there will be a radical shift in the way that regulatory business will be done."
>
> **DR. LISA JENKINS** / CSC Life Sciences

> "The law, implemented the right way, can provide the resources and create the path by which more quality therapies will find their way to market."
>
> **TERRY HISEY** / Deloitte

Addressing Risk-Benefit

The new law also provides provisions for a more formal process for risk-benefit evaluations for new medications, which includes integrating patient perspectives. Experts say the agency will collect quantitative and qualitative data from patients and possibly patient caregivers and/or advocacy groups.

Diane Berry, VP of government affairs and global health policy at Sarepta Pharmaceuticals, says Congress recognized there were unmet medical needs and there was a need to provide new approval mechanisms and expand existing ones to speed drug development and approval, which they did by extending the accelerated approval path to rare diseases.

"Congress made it more flexible to use surrogate endpoints," she says. "Congress was explicit about the FDA using this pathway for rare diseases and factoring in the severity and rarity of the disease, as well as the patient perspective. The FDA also is initiating a patient-focused drug development initiative, and regulators have started consultations with the patient stakeholder community. They've started with a list of 20 disease areas to focus on, and they're going to continue to be meeting with stakeholders to understand how best to capture their perspective to help frame and put into context these regulatory decisions."

The FDA is expected to hold hearings and provide access for patients with various diseases and help them understand the trade-off in terms of risk benefit, Dr. Siegel says.

"We work with patient groups to help us understand what is important to them, how they view different medication profiles, and what's important to them in terms of disease symptoms as well as side effects so that we can develop targeted product profiles and know if our product is meeting their needs," he says. "The new provisions that support FDA adoption of frameworks for risk-benefit assessment will lead to increased transparency, so everyone can understand how decisions were made, how different factors were weighed, what the factors were, and what trade-offs were made. This process helps identify what is known and what isn't known, it uncovers where the uncertainty is, and helps identify what more needs to be known. All of this data should lead to better justified decisions, better labeling, better communication of risk, and better drug development by developers."

Mr. Fox says the next great breakthrough will be when the law catches up with the industry on combination products, drug-drug combinations, as well as drug-device, biologic device combinations.

"One important positive is the momentum that PDUFA V could create by increasing first cycle approvals for new medications," Mr. Fox says. "One blind spot continues to be that we are still looking at therapies as either drugs or biologics or devices. So many of the newer products are drug-device dependent. These combination products still cross organizational and statutory lines within the agency." PV