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# Pharmaceutical Regulations *Become More* CHALLENGING

As pharmaceutical regulations become more complex globally, regulatory professionals are challenged to stay abreast of new regulations to remain compliant.

Now more than ever, global health authorities are looking for a comprehensive risk management plan that includes not only all of the elements of regulatory compliance, but ties to the company's plan for sales, marketing, and overall brand protection, our experts say.

"Deeper involvement by the regulatory professionals in the overall product launch strategy earlier in the development stages of the product helps pharmaceutical companies demonstrate to health authorities their commitment to the safety of consumers, affording a better chance at a smooth registration process," says Michael O'Gorman, CEO of Sentrx.

According to Mr. O'Gorman, the regulatory affairs department is involved in product development, manufacturing, registration, postmarketing activities, and lifecycle optimization.

"This is already a heavy burden on regulatory affairs professionals who undertake a variety of responsibilities throughout their companies," he says. "Pharmaceutical companies will continue to look for top talent in regulatory affairs to not only be the guardians of compliance, but to ensure the best success for the company's products.

"With constantly changing global regulations, regulatory affairs professionals will have to have access to the best available resources,

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>
> **MICHAEL O'GORMAN** / Sentrx

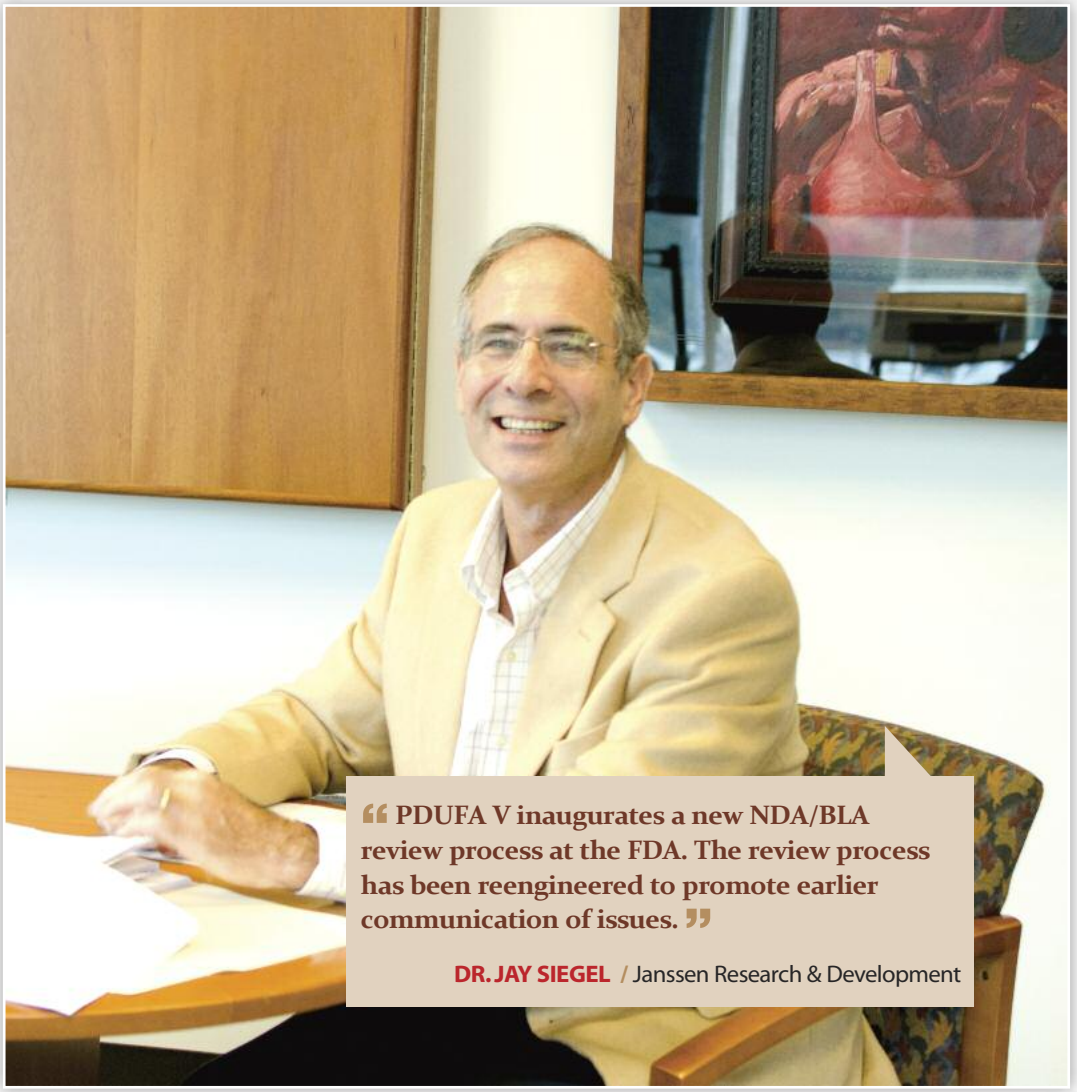
### Results of PDUFA IV

Drug sponsors experienced a mixed regulatory burden under the FDA Amendments Act, which was also the fourth iteration of the Prescription Drug User Fee Act (PDUFA IV), according to recent research from the Tufts Center for the Study of Drug Development.

The analysis found that, since 2007, the regulatory burden decreased for new drug applications (NDA) and biologics license applications (BLA) approvals, but increased for supplemental new drug applications (sNDA) and biologics license approvals (sBLA), while regulatory outsourcing by sponsors also increased.

**Other findings:**

- Spending on outsourced regulatory services by developers rose 167% between 2007 and 2010.
- The difference between optimal and sub-optimal sponsor experiences with the FDA review process was less for NME/new BLAs than for sNDA/sBLAs.
- Ten of 21 regulatory activity variables were considered significant by sponsors, when optimal and sub-optimal approvals were compared on a disparity index.



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> **DR. JAY SIEGEL** / Janssen Research & Development

therefore evolving into experts in procuring people or service providers and deploying those resources toward critical company initiatives," Mr. O'Gorman continues.

A recent study by Cutting Edge Information finds that top 50 pharmaceutical companies have increased their regulatory affairs budgets by an average of 27% since 2010. Small drug manufacturers, as well as medical device companies, also increased their regulatory affairs budgets during the same timeframe.

Regulatory affairs groups continue to grow in prominence within the pharmaceutical industry, garnering greater budget resources along the way. The largest pharmaceutical companies have experienced the highest regulatory affairs budget increases among surveyed companies since 2010: $5 million.

The Cutting Edge study also found that growing pharmaceutical companies dealing with larger portfolios tend to decentralize their regulatory affairs groups in pursuit of geographic or therapeutic specialization. But in the long run this results in a lack of uniformity and difficulty communicating across branches.

**FAST FACT**

THE TOP 50 PHARMACEUTICAL COMPANIES HAVE INCREASED THEIR REGULATORY AFFAIRS BUDGETS BY AN AVERAGE OF 27% SINCE 2010.

Source: Cutting Edge

A concise regulatory strategy is key during the project planning stage and is integral in understanding how to implement project requirements in the plan to ensure regulatory compliance with global market requirements, says Debbie Thomas, global VP, regulatory affairs, at West Pharmaceutical Services.

"This regulatory strategy should be a critical driver throughout the product lifecycle," she says. "The efficiency of a drug or device registration, license, or marketing authorization begins at the genesis of the development process. It is vitally important for regulatory compliance in the early stages of the drug and device development process, throughout all phases of clinical trials, process transfer, marketing authorization, and continuing through postmarket surveillance activities."

As regulations continue to change and evolve, Ms. Thomas says the regulatory professional needs to stay abreast of the latest requirements and expectations including updates, changes, and interpretations.

"The growth in the development and use of combination products is an area that appears to be very complex and challenging," she says. "As regulations become more specific and inclusive of the complex nuances of combination products, the ability to navigate and articulate the regulatory strategy is imperative for success. It is vital that regulatory affairs professionals understand the intimations of how the regulations are applicable to these types of products."

## New Regulations: PDUFA IV

In July the Prescription Drug User Fee Act

## European Regulations

Compliance with European Medicines Agency's EudraVigilance Medicinal Products Dictionary (EVMPD), which became mandatory in July 2012, is critical, says Gillian King, head of global consulting, global professional services, at CSC Life Sciences.

The latest regulations (the latest format being the XEVMPD) require marketing authorization holders to submit comprehensive medicinal product data for all products for which they hold the license for human use in Europe.

"The mandate also requires that any existing EVMPD records that have already been submitted are brought up to date," she says. "This means that a substantial amount of accurate information must be collated, sent, and kept current. The existence of the dictionary helps minimize the threat to human health in the event of a problem with a specific batch of product, enabling products to be quickly traced back to the source and facilitating speedy recalls."

Another important European regulation is the Clinical Trial Directive, introduced as law in 2001 but still evolving with new proposed changes impacting how clinical trials will operate in Europe in the coming years. The latest phase requires a much more detailed profile of a product before it gets to market and harmonizes clinical trial requirements, all with the aim of protecting public health in a consistent manner across all EU countries.

The transition to the electronic common technical document standard (eCTD) for drug applications and updates continues, again ensuring that content is submitted and handled efficiently in a digital format that is easily searchable, thanks to intelligent indexing. The new Regulated Product Submission (RPS) standard — or eCTD version 4 — aims to take eCTD to the next level. The goal is to introduce greater flexibility and more robust capabilities, because the original specification has certain limitations.

Ms. King says these requirements have a vast impact on life-sciences companies.

"Time is being taken away from front-line work as information management becomes a necessary evil," she says. "In some cases, as much as 80% of regulatory resources are being expended on regulatory administration, including information maintenance, because of the increasing demands around safety compliance auditing. The key for the industry is to seek out compensatory gains from the upheaval, for example taking advantage of the ability to streamline processes and share content more readily as they digitize it."

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> **DEBBIE THOMAS** / West Pharmaceutical Services

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> **NICK COLUCCI**
> Publicis Healthcare Communications Group

(PDUFA V) was enacted. The law, which became effective Oct. 1, 2012, reauthorizes the FDA to collect user fees for brand-name prescription drugs and medical devices and creates user fee programs for generic drugs and for biosimilars.

The law includes more than $700 million in fees related to brand-name drugs for fiscal year 2013 alone. For generics, the generic drug industry would pay about $1.5 billion for fiscal years 2013 to 2017.

PDUFA will have a substantial impact on drug development, says Jay Siegel, M.D., chief biotechnology officer, and head, global regulatory affairs, at Janssen Research & Development, part of the Janssen Pharmaceutical companies of Johnson & Johnson.

"PDUFA V inaugurates a new NDA/BLA review process at the FDA," he says. "The review process for new products has been reengineered to promote earlier communication of review issues. Two months have been added to the initial review cycle, providing more opportunity to resolve issues arising in the review, advisory committee discussions, or inspections without extensions or additional cycles. Used correctly, this process has potential to bring safe and effective drugs to patients considerably faster."

Nick Colucci, president and CEO of Publicis Healthcare Communications Group, points out that PDUFA V provides for a 6% increase in fees collected.

"Equally notable, it aims to increase accountability and streamline the review process with improved communications, including a commitment to increased FDA availability for early-stage meeting," he says.

Ms. Thomas says one section of PDUFA V — Section 707 — promotes pharmaceutical supply chain integrity by expanding import authority and visibility.

"Additionally, Section 809 in the Act supports the sharing of information with other regulatory agencies to enhance the safety and quality of the drug supply," she says. "The act should enhance drug development in the future because it is intended to provide more FDA communication with sponsors during drug development and review; establish more efficient processes; provide greater consistency across FDA review divisions; and establish

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> **CHRIS GARABEDIAN** / Sarepta

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>
> **SHEILA ROCCHIO** / PHT

more transparent risk evaluation and mitigation standards."

PDUFA V is expected to benefit rare diseases as well, says Chris Garabedian, CEO of Sarepta.

"PDUFA V is one of the most important regulatory advances for rare diseases since the Orphan Drug Act of 1983, as it allows for and promotes accelerated access for patients to new therapies and accelerated development of promising therapies," he says. "Given the industry's increased focus on rare diseases in recent years, those of us working to address this underserved area in drug development are, of course, interested to see how the FDA will apply, in a real-world setting, the flexibility offered to them by this new legislation. If applied as the legislation seems to call for, we as an industry are going to have a tremendous opportunity — and increased responsibility — to make a difference in the lives of patients with serious diseases and no current treatment options."

Mr. Garabedian says in an era where the FDA has taken its share of criticism for being highly risk averse, perhaps to the detriment of therapeutic innovation and particularly for more prevalent and high-profile diseases, the agency's stance in the area of rare and life-threatening diseases will give it a real opportunity to truly transform the lives of many patients and their families.

## Standards Become Important

Experts say life-sciences organizations that haven't kept up with the latest requirements will find themselves at a disadvantage, and they be unable to get products to the market within an acceptable timeframe, our experts say. Increasingly, there is a push for standardization and electronic submissions of critical content.

The FDA, CDISC, and C-Path are collaborating on efforts to support development of therapeutic area standards. One new development is the creation of the Coalition for Accelerating Standards and Therapies, known as CFAST, an initiative to accelerate clinical research and medical product development by creating and maintaining data standards, tools, and methods for conducting research in therapeutic areas that are important to public health.

This partnership will help to accelerate clinical research by determining best practices and using standards more quickly than on the current path before this effort, says Neil de Crescenzo, senior VP and general manager at Oracle Health Sciences.

"As broader collaboration and the generation of insights from big data become essential parts of the new clinical trial process, data standardization reduces the need for custom development and enables faster implementation of solutions," he says. "The biggest challenges related to creating standards for clinical research include determining which organization across the ecosystem will have the responsibility and authority to make these determinations, and what people from what organizations should be involved in these effort."

Additionally, Ryan McGuire, research team leader at Cutting Edge Information, says the surge in retrospective health outcomes studies demand uniform data collection in order to make accurate comparisons across multiple clinical trials.

"Without data standardizations, comparing outcomes becomes more time consuming," he says. "Also, analytic software is growing more powerful, but its true potential cannot be reached unless multiple, uniform data sets can be entered efficiently."

Sheila Rocchio, VP of marketing and product management at PHT, says clinical trials are like snowflakes: no two are ever exactly alike, even in the same indication.

"Standards provide a consistency across therapeutic areas that can accelerate the trial in terms of the types of information that are collected, the way the information is collected, and what kind of interaction the sites can expect," she says. "They can shorten the learning curve, make data transfer and review of regulatory components faster and easier, and get technology systems up and running faster."

Integrated regulatory compliance management implies that both the over-arching business processes and the supporting IT systems and technology are aligned, and that there is true automation across the process, says Adam Sherlock, director of life sciences, CSC.

"Get these two things right and the business function of creating, obtaining, and maintaining successful product registrations will naturally become far more efficient," he says. "Systems integration between the three key tools used in regulatory — content management, submission publishing, and regulatory information management — eliminates substantial effort in duplicated data entry, data management, and coordination. It enables process automation and smoothes out the disconnect between discrete functional activities, which normally adds delay." PV