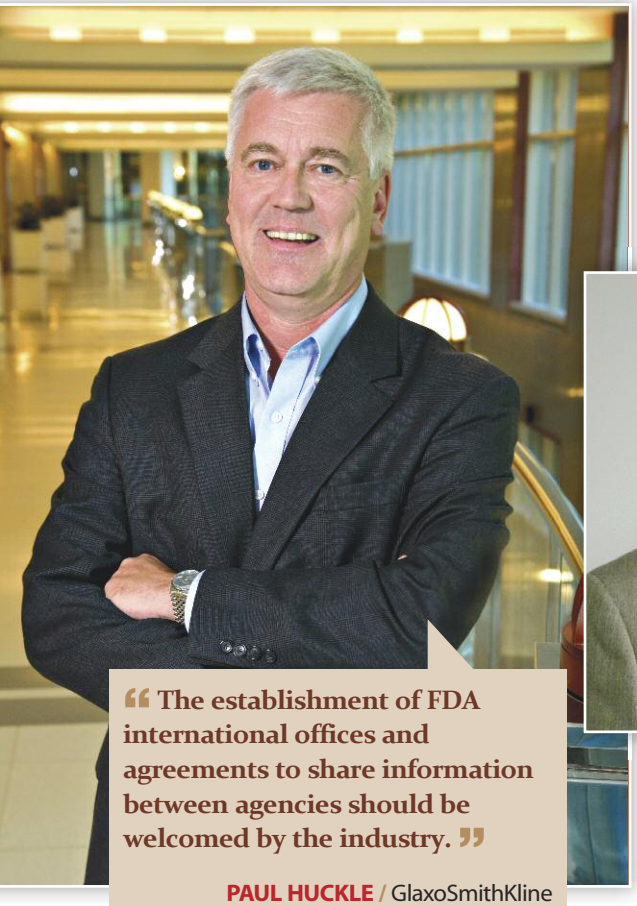
Denise Myshko

GLOBAL *Regulatory* Oversight

Growing regulatory requirements, continued standardization of submission and data requirements, and a continued focus on safety are just a few of the issues facing pharmaceutical companies.



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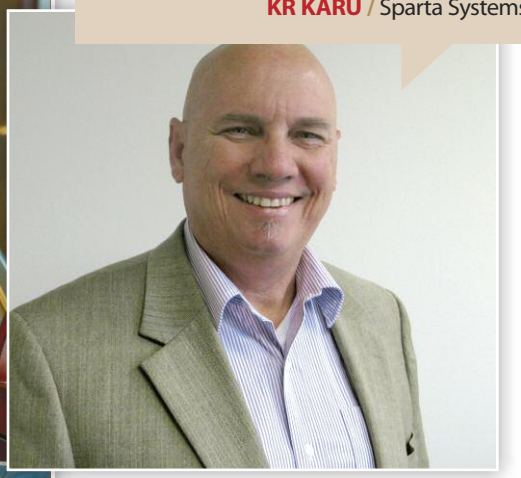
PAUL HUCKLE / GlaxoSmithKline

"With the FDA's recent acceptance into PIC/S, an international agreement between countries' regulatory agencies, inspection information will now be shared between the agencies."

KR KARU / Sparta Systems



Globalization is changing the regulatory environment for the pharmaceutical industry. About 80% of the active pharmaceutical ingredients in medications sold in the United States are manufactured elsewhere, according to the FDA. Imports of pharmaceutical products have increased at almost 13% and imports of devices have grown at more than 10%. Between 2007 and 2015, the FDA estimates that imports of all FDA-regulated products will triple, to a 15% growth rate.

As a result, the roles of the various regulatory agencies are changing. In the United States, the FDA is developing plans to address the safety of products on a global basis and in response to increasing globalization, the agency has expanded its capabilities and regulatory authority. The agency also has opened additional offices throughout the world and increased the number of foreign inspections. Inspections of overseas drug manufacturing plants, for example, increased from 333 in 2007 to 424 in 2009.

In light of these changes, experts say companies need a broad, comprehensive global view of regulatory affairs and to have a development strategy that focuses on the needs of multiple stakeholders globally, including regulators, practitioners, consumers, and payers.

There is a growing need for companies to have a comprehensive strategy in place that bridges the regulatory, development, and commercial marketing functions, to serve as a key driver for product development and decision support in all stages," says Dr. William Jacobson, executive director, U.S. strategic regulatory services, OptumInsight Life Sciences.

"To accomplish this, comprehensive regulatory and risk management strategies are critical and must be developed and implemented as early in development as possible," he says.

Dr. Jacobson adds that life-sciences companies will be required to be better prepared for supply-related safety and efficacy issues.

"Pressure is growing for pharma companies and regulators to absolutely ensure and enforce potency and safety and to protect the manufacture and delivery of ingredients and products as they move throughout their respective supply chains, wherever they may be developed and manufactured," he says. "There is a strong trend now toward regulatory harmonization among regulatory bodies throughout the world."

Denise (DeeDee) DeMan, founder, chairman, and CEO of Bench International, says pharma companies have to have a broader definition of regulatory affairs.

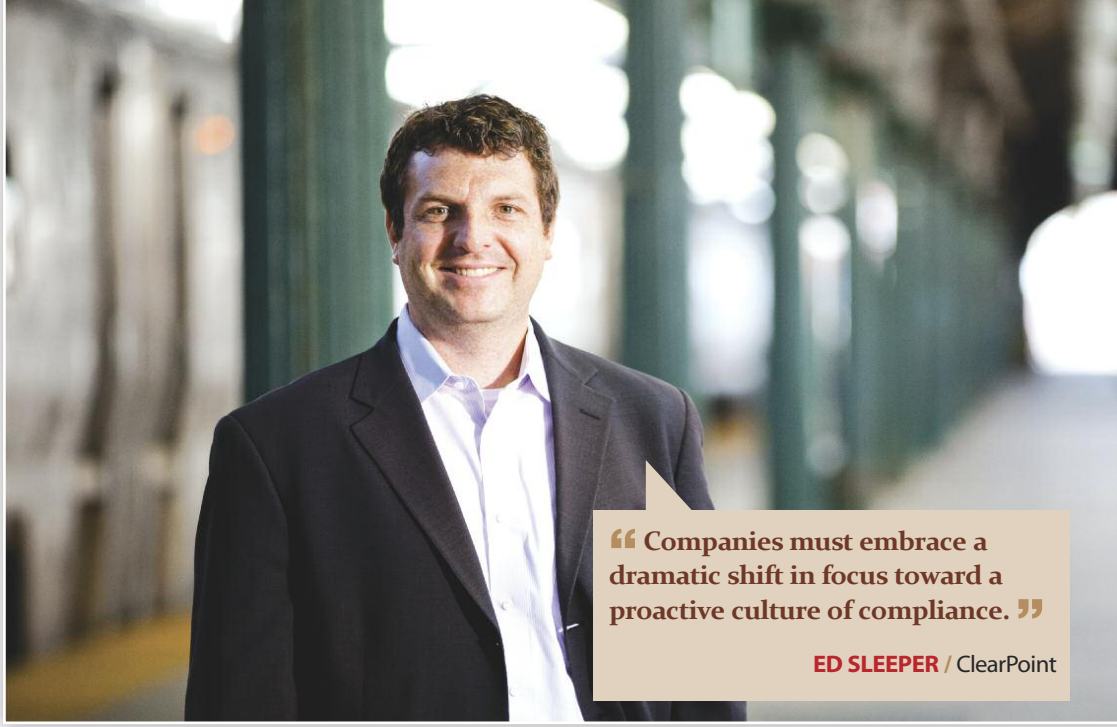
"It is no longer a 'registration' process, but a multipronged and complex system from target to access to market," she says. "The function is responsible for ensuring as safe a landing as possible for its molecules and shareholder investments. Too often, regulatory leadership neglects to think about the downstream effect of drugs once they're used in real-world settings. Trials fail, endpoints are missed, desired labels remain only dreams, and drugs aren't reimbursed. Getting pharma companies to recognize the importance of a forward-looking regulatory function is a monumental challenge in and of itself."

The FDA's Safety Initiative

The Food and Drug Administration is developing an international operating model that relies on enhanced intelligence, information sharing, data-driven risk analytics, and the smart allocation of resources through partnerships. The new approach rests on four core building blocks:

1. The FDA, in close partnership with its foreign counterparts, will assemble global coalitions of regulators dedicated to building and strengthening the product safety net around the world.
2. With these coalitions, the FDA intends to develop a global data information system and network in which regulators worldwide can regularly and proactively share real-time information and resources across markets.
3. The FDA will continue to expand its capabilities in intelligence gathering and use, with an increased focus on risk analytics and thoroughly modernized IT capabilities.
4. The FDA will effectively allocate agency resources based on risk, leveraging the combined efforts of government, industry, and public- and private-sector third parties.

Source: Food and Drug Administration.
For more information, visit fda.gov.



> "Companies must embrace a dramatic shift in focus toward a proactive culture of compliance."
>
> **ED SLEEPER** / ClearPoint

Recent FDA Initiative

In its report, Pathway to Global Product Safety and Quality, the FDA is recommending a dramatic shift in strategy. The report calls for the agency to act globally to help ensure safety and quality of imported products, including forming partnerships with regulatory agencies around the globe.

The FDA is developing an international operating model that relies on enhanced intelligence, information sharing, data-driven risk analytics, and the smart allocation of resources through partnerships.

"Effectively this means that the FDA understands that as a whole the pharma industry is becoming increasingly global and the agency is taking the necessary steps to ensure that its regulatory directives account for this globalization," says KR Karu, industry principal, Sparta Systems.

"For pharma companies, most of which now operate in and source ingredients from multiple countries, this means that, more than ever, they need to align their processes for managing quality and compliance with directives are standardized across the organization," Mr. Karu says. "With the FDA's recent acceptance into PIC/S, an international agreement between countries' regulatory agencies, inspection information will now be shared between the agencies, providing the FDA with a more global set of eyes and ears."

Paul Huckle, chief regulatory officer at GlaxoSmithKline, points out that the industry has been globalizing product manufacturing and supply chains for some time now, but most regulatory agencies are still largely operating national approaches to regulatory inspection.

"The need for more efficient use of both agency and industry resources through harmonized standards, international cooperation, and mutual recognition of inspections is needed," he says. "The establishment of FDA international offices and agreements to share information between agencies should be welcomed by the industry as initial steps in this direction. Joint inspections of foreign manufacturing facilities by the FDA and overseas agencies can be conducted to build inter-agency trust, leading ultimately to the recognition by the FDA of inspections conducted by foreign agencies. Given the large volumes of medicines that are supplied to the United States from the rest of the world, and the FDA's standing as a leading regulatory authority, they are well placed to take a global leadership position in this area."

Addressing Challenges

Doreen Lechner, Ph.D., executive VP, pharmacovigilance client services, Sentrx, says pharma companies will need to re-evaluate their antiquated R&D environment to bring safe and effective products to market in a more efficient and cost-contained manner.

"Pharma coalitions as well as multidisciplinary teams within the individual pharma company will need to be established to assess and progress through the paradigm shift in strategy," she says.

Dr. Lechner says since regulations throughout the world are not aligned, pharma companies are trying to keep abreast of the individual regions and national laws, making it costly and difficult to establish a unified approach to get a product through its development life cycle.

"To address these challenges, pharma companies need to keep adherence, risk profiling, and innovation at the forefront," she says.

Ed Sleeper, director, compliance and catalog practice area, ClearPoint, says companies must embrace a dramatic shift in focus toward a proactive "culture of compliance."

"This is achieved via a combination of consistent guidance and communication from leadership; strategic blended training solutions that foster positive behavioral changes; and an overall commitment to compliance from a company mission and values standpoint," he says. "Life-sciences companies must proactively ensure that their regulatory compliance policies and procedures are up-to-date, and that their employee and third-party training is changing behavior — the all too prevalent tick-the-box mentality is no longer sufficient and serves to dramatically increase risk for organizations."

Dr. Lechner says risk profiling is critical to managing products through the development cycle and maintaining market share once a product is on the marketplace.

"Pharma companies need to change their view of safety, beyond the transactional safety of meeting regulatory deadlines and integrate safety into the entire benefit/risk profile using a cloud approach," she says. "Companies need to constantly evaluate alternatives to reach the marketplace with more effective products, technologies, and processes to advance in areas of personalized medicine. Innovation is critical

through life-cycle development and to building alliances with regulatory agencies in the hope of reducing costly regulatory hurdles."

Mr. Huckle adds that a scientifically based and transparent approach to the quantitative assessment of benefit/risk needs to be developed and implemented widely.

"The current approach is largely empirical and can lead to unnecessarily different regulatory outcomes between agencies," he says. "This lack of predictability introduces additional uncertainty that can dissuade industry from developing potential treatments, particularly in new areas. By adopting a more standardized approach, acceptable margins of safety and efficacy can be discussed and agreed

SOUND BITES FROM THE FIELD

The Top Trends Impacting the Regulatory Arena

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1. The FDA's recent Guidance on Risk-Based Approach to Monitoring clearly encourages the industry to develop a risk-based monitoring approach for all phases of clinical trials rather than the current widely accepted practice of 100% source-data verification during on-site monitoring in all but late-phase clinical trials.

2. The guidance recommends that each sponsor conduct a risk assessment of the specific human subject protection and data integrity risks associated with the complexity of the study design as set forth in the study protocol.

3. The monitoring plan should be tailored in accordance with these risks with an appropriate mix of centralized and on-site monitoring practices and should include a description of how to manage noncompliance, training, and study-specific information along with predetermined triggers for updating the plan.

NICK COLUCCI is President and CEO of Publicis Healthcare Communications Group (PHCG), a health-oriented agency network. For more information, visit publicishealthcare.com.

1. The current global economic crisis is changing the way products are reimbursed, which will have an enormous impact on funding future innovation. Whether it is the looming 2% across the board cuts if the U.S. congressional super committee fails or Greece's failure to pay companies for the past three to four years, innovation will suffer.

2. Regulatory scrutiny within the postlaunch environment continues to increase and is shifting the risk-benefit ratio for drug development and increasing the need for comparative effectiveness research.

3. The biosimilars pathways will change the way people develop biologics; but make no mistake — these aren't generics. The pathways will allow the biggest biologics players to make investments that may create "biobetters."

PHILIP LEE is President and CEO, PHT Corp., a provider of ePRO solutions for clinical trials and postmarketing studies. For more information, visit phtcorp.com.

1. A large trend in direct-to-patient trials is emerging. "Siteless" trials reflect the sponsor's need to reduce the burdensome cost of clinical trials. For sponsors that want to conduct direct-to-patient trials, ePRO technology is ideal. By providing patient-centric technologies or Web-based diaries for data collection, ePRO solutions capture the voice of the patient. Only ePRO can give sponsors an accurate and real-time view of a drug's efficacy without distortion and recall bias. Sponsors benefit from leveraging ePRO to make faster, more accurate decisions regarding their product portfolio. What's better than asking the subject, the intended end-user, how a drug works before it enters the market?

2. Clinical research technologies, such as ePRO, are increasingly prevalent in the industry for a few reasons: market adoption, safety monitoring, and the need for higher quality clinical data outcomes. These trends are reinforced by the FDA PRO Guidance. The final guidance recommends sponsors begin PRO or ePRO instrument development and evaluation early in medical product development and should also engage the FDA in a discussion about a new or unique PRO or ePRO instrument before confirmatory clinical trial protocols are finalized.

3. The life-sciences industry is now recognizing the real necessity to integrate innovative technologies to help minimize the escalating costs associated with bringing new drugs to market. Leveraging efficiencies associated with e-clinical technology is fundamental in today's market. Pharmaceutical companies that embrace technology to collect PRO enjoy increased compliance and time stamped, high-quality clinical trial subject data. This is especially important when PRO data are the primary endpoint or required for labeling claims.

JAMES ROGERS is CEO Nextrials Inc., a provider of clinical research software and services. For more information, visit nextrials.com.

1. As the industry has progressed with the development of technologies to eliminate paperwork from clinical trials, more and more source data are electronic in nature. The industry has been hesitant to use eSource data as it has the potential to be copied or changed without a clear audit trail of the event. These concerns can be easily remedied but, until now, the industry has delayed implementation until regulatory authorities could outline the parameters under which they would accept eSource data. These documents provide that regulatory guidance to sponsors, CROs, and investigators for ensuring the reliability, integrity, and traceability of electronic source data and source records.

2. Under its proposed guidelines, the FDA outlines several scenarios for how eSource data might be gathered, including from a patient's electronic health record. This is good news for us and others in the industry that have long worked toward establishing and implementing integration standards for electronic data capture platforms with EHR platforms. An integrated EDC/EHR platform is the key to capturing routine data already collected as part of patient care and any additional data unique to the clinical trial. With these new guidances, the FDA and EMA are continuing to demonstrate their willingness to accept electronic data as valid study documentation.

3. By fully using eSource data and, in particular, an integrated EDC/EHR tool, pharmaceutical R&D can dramatically reduce its costs and timelines by taking advantage of larger potential subject pools for faster study starts and reducing the level of on-site source data verification required.

ANGUS RUSSELL is CEO of Shire, a specialty biopharmaceutical company. For more information, visit shire.com.

1. Health technology assessment (HTA) or comparative effectiveness: In Europe the increased collaboration between EMA and national HTA bodies to facilitate assessments of drugs' clinical value and relative effectiveness is being institutionalized. Early dialogue with payers will impact clinical trial development to satisfy requirements of the fourth hurdle. The other three hurdles being safety, efficacy, and quality. In the United States, one sees a growing emphasis on comparative effectiveness as evidenced by the establishment of PCORI, although the focus of the

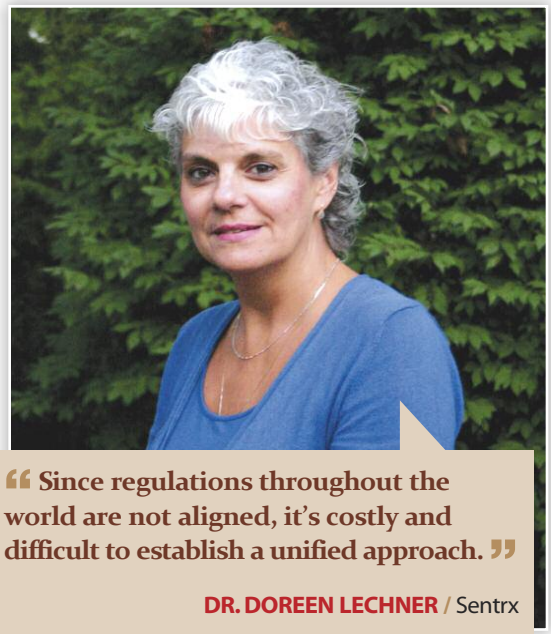
between key stakeholders, thereby encouraging more investment in innovative treatments. Industry, regulators, and academia need to work together to develop and implement these assessment tools."

Companies need to take a thorough look at the processes they have in place to manage these functions, identify where improvements can be made, and take the necessary steps to make these improvements, Mr. Karu says.

"For many, this means automating quality processes and the collection of data associated with them, and centralizing the management of these functions to ensure organization-wide compliance," he says. "Companies need to break down the silos between sites and business functions. This will provide companies with quick and easy access to the data they need to report to the FDA and a comprehensive system for reporting it, while minimizing risk associated with managing a broad supplier network and instituting organization-wide changes that can have a positive impact on their businesses."

Melonie Warfel, director, life sciences industry solutions at Pegasystems, says for life-sciences companies to be successful, they need to develop processes and implement technologies that allow them to ensure more effective compliance to new and ever-changing regulations.

"These technologies must be agile and provide an environment in which changes can be made rapidly without a lot of overhead or lag time," she says. "Additionally, these technologies must be able to monitor and flag events that could potentially result in noncompliance. For example, one area for improvement is clinical trials. Organizations need to do a better job collecting, managing, and analyzing adverse events during and after clinical trials. Those companies that excel in this can shorten the timeline for conducting successful trials and improve post-approval management of safety information." PV



> **"Since regulations throughout the world are not aligned, it's costly and difficult to establish a unified approach."**
>
> **DR. DOREEN LECHNER** / Sentrx

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institute is not drug cost. In the United States, it's become necessary to talk with payers about the value of drugs that are still in development.

2. Prescription Fee Authorization Act (PDUFA): In the United States, PDUFA is up for reauthorization in 2012. The negotiations between the industry and the FDA are going well. Given that the reauthorization is scheduled to take place during an election year in the United States, it would be great for it to be done in the late spring or early summer of 2012.

3. Implementation of the pathway for biosimilars: The approval process in both Europe and the United States is still evolving. In Europe where the pathway has been established and a few products have been approved, guidance documents are still being issued. In the United States the FDA is getting ready to release its guidance. As science progresses the pathway will evolve.

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1. The Obama Administration has outlined plans to achieve $320 billion in healthcare savings over a decade, which includes requiring drugmakers to provide $135 billion in discounts on medicines supplied under the Medicare prescription drug benefit; banning "pay-for-delay" deals between brand-name and generic drug makers that delay the entry of generics onto the market; and reducing market exclusivity on biologic drugs from 12 years to seven years.

2. Measures for Medicaid included in the proposals, and aimed at saving $66 billion over the decade, include: requiring manufacturers that improperly report items for drug coverage under the program to fully repay states; tracking high prescribers of prescription drugs in Medicaid; enforcing the program's drug rebate agreements; increasing penalties on drugmakers for fraudulent noncompliance with the rebate agreements; and requiring drugs to be properly listed with the FDA to receive Medicaid coverage.

EXPERTS

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