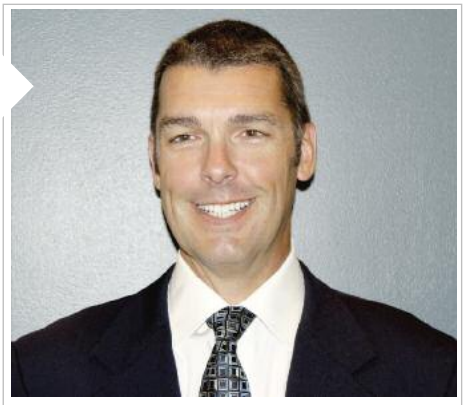
# Regulating THE GLOBE

Carolyn Gretton

*The growing pressure on pharma companies and regulators to ensure and enforce product potency and safety has resulted in a strong trend toward harmonization among regulatory bodies throughout the world.*

*"Regulatory professionals can no longer operate with a local-only mentality; every product and regulatory decision must consider a global perspective."*



**DR. MARK DE ROSCH**
*Inspiration Biopharmaceuticals*

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

According to Sherry Keramidas, Ph.D., executive director of the Regulatory Affairs Professionals Society (RAPS), the FDA's recent increased focus on operations outside the United States is a logical response to the globalization of the healthcare product sector. However, she notes, emphasis on international operations is nothing new to the regulatory profession.

"RAPS' Scope of Practice research shows that regulatory professionals have been taking complex global considerations into account for more than a decade," Dr. Keramidas says. "This trend of involvement in multiple regions worldwide initially was evident among those working in industry; however, more recently we have seen this multinational focus among professionals working in government, consultancies, CROs, and research organizations."

"Just as drug development has gone global, with significant clinical and pharmaceutical manufacturing activity taking place in India, China, and South America, the FDA has recognized that its control of product safety and product quality must also go global," says Mark De Rosch, Ph.D., VP, regulatory affairs, at Inspiration Biopharmaceuticals. "The FDA's presence with offices in foreign countries puts the agency in closer contact with regulators in those countries than ever before, driving these relationships in collaboration."

As the FDA expands its relationship with international regulatory agencies, Len Lescosky, divisional VP, chemistry, manufacturing and controls, regulatory affairs, for Abbott's Pharmaceutical Products Group, stresses the need for pharma companies to be prepared by optimizing their global information systems to better track and respond to agency questions.

"Although companies will continue to harmonize product labeling and supply chains, specific individual country legal and regulatory requirements may prevent full harmonization," Mr. Lescosky says. "Therefore, companies should be able to quickly and concisely explain the differences among their products."

"Responses to questions from one agency need to be consistent with responses to other regulatory agencies, as this information may be shared across countries," Dr. De Rosch says. "Sponsors will need to develop mechanisms to track responses to questions and revisions to documents in the marketing applications and assess impact to other applications."

Lawrence Liberti, executive director of CIRS — the Centre for Innovation in Regulatory Science, says his organization has found that having a common framework for the assessment of the benefits and risks of medicines can be a valuable decision-making tool within a company.

"A common framework allows people to put their thoughts down in a standardized fashion and compare those thoughts; they may disagree, but at least they've been able to explain in a detailed way how they feel about where the product stands at any point in time with regard to fulfilling its profile and what its benefits and risks and value should look like," Mr. Liberti explains. "This also allows the company to clearly present the information to agencies around the world that have accepted the commonality of the decision-making framework."

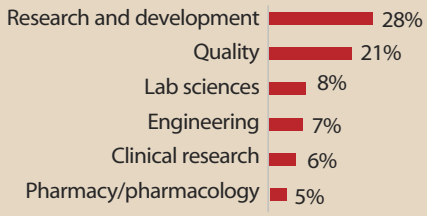
Dr. Keramidas sees regulatory professionals tracking regulations and regulatory issues in multiple regions and building regulatory strategies to reflect requirements in those regions as a wat to accommodate globalization.

"An important part of the regulatory professional's role is looking at the most effective approach for clinical trials and registration that will allow product launches in multiple markets," she says. "It is equally important that the regulatory strategy also address the international supply chain, manufacturing in different countries and regions, and compliance and surveillance needs."

Dr. De Rosch says the FDA, by necessity,

### Prior Professional Experience

The vast majority of regulatory professionals (96%) did not begin their careers in a regulatory position. Most transitioned through one or more areas of work before moving into regulatory. On average, regulatory professionals have eight years of "other" professional experience prior to a regulatory position, with slightly less "other" professional experience among those based in Europe (six years) and Asia (five years).




Source: RAPS, 2012 Scope of Practice & Compensation Report for the Regulatory Profession.
For more information, visit raps.org

**LAWRENCE LIBERTI**
*CIRS*

*"With the advent of health technology assessment (HTA) reviews, agencies are expecting that the pharmacoeconomic value, the beneficial difference between a new product and existing therapies, be clearly defined and explained."*

will be involved in modernizing the global regulatory environment through sharing of inspection skills, product safety assessment, and good clinical practices (GCPs), to the benefit of both U.S. and global pharma.

"With these advances, a manufacturing or clinical site in a remote area of China will be just as accessible to the FDA as a manufacturing or clinical site in New Jersey," he says. "Though this may complicate things for the pharma industry in the short term, in the long term there should be an overall improvement in product quality and safety."

Key elements of international regulatory strategy and implementation, according to Dr. Keramidas, include tracking regulatory considerations, using a strategic and critical thinking mindset to work across borders, and developing effective communication with colleagues in different regions.

"Communication is particularly important in this global environment, as expertise and knowledge of the important cultural, economic, and legal nuances of different regions is often spread among multiple team members, often in disparate locations," she adds.

## Diverse Disciplines

According to Mr. Liberti, the multidisciplinary regulatory teams within the pharma industry are being shaped by several trends, chief among them the need to address the so-called "fourth hurdle" of market access by demonstrating product value to payers and providers.

"With the advent of health technology assessment (HTA) reviews, these agencies are expecting that the pharmacoeconomic value, the beneficial difference between a new product and existing therapies, be clearly defined and explained," Mr. Liberti says. "With so many national payer agencies and even private insurers having limited budgets, they want to be sure that the medicines they're paying for have real value."

As a result, Mr. Liberti says, HTAs are now becoming an important overall component of medicine development, with more pharmaceutical companies addressing HTA needs early on in their development programs.

"What that means is they're integrating health economics and outcomes research specialists into the project team from the earliest phases of drug development because now, in addition to proving quality, safety, and efficacy, sponsors need to be sure their development program can support the value of the medicine," he adds.

Mr. Lescosky believes the key to building a successful multidisciplinary team is to select members who bring with them a broad understanding of the drug development and commercialization process and significant experience in non-regulatory roles.

"A broader understanding of the business helps these teams to effectively work together to both navigate the procedures and expectations within their own organization, as well as meet the requirements of the regulatory process," he says. "Additionally, the team leader must be able to align the objectives of a number of internal groups, so having an understanding of the different aspects of the overall process is critical in achieving success."

To be effective in the regulatory arena, Dr. Keramidas says pharma professionals with broad non-regulatory experience have to make some adjustments in how they approach a product, as well as develop the ability to look at the full life cycle and the legal, regulatory, scientific, public health, and business dimensions of products.

"Regulatory professionals must have a solid understanding of the science and technology that forms the foundation for new products; an understanding of the product life cycle and the regulatory requirements at each stage; and effective communication, negotiation, and critical thinking skills," Dr. Keramidas says. "They also need to think strategically and anticipate issues and problems and try to address these as early in the process as possible."

Dr. Keramidas also stresses the ability to understand regulations in multiple regions and the importance of connecting regulatory staff around the globe.

"In many organizations, the regulatory team members working in locations away from the headquarters sometimes feel less connected to the team," she observes. "There is strong demand for qualified regulatory professionals right now, and RAPS research suggests that many professionals are being recruited to new organizations, underscoring

### Compensation on the Rise for Healthcare Regulatory Professionals

Regulatory professionals are highly valued by companies in the life-sciences and healthcare products sector, and they are being rewarded with increased compensation for the increasingly varied, vital work they perform.

The 2012 Scope of Practice & Compensation Report for the Regulatory Profession from the Regulatory Affairs Professionals Society (RAPS) found that regulatory professionals' base salary and total compensation grew in the United States, Canada, and some European countries despite a tough global economy and workforce cutbacks in areas such as pharmaceuticals. In North America, base salaries increased by 4%, and total compensation grew by an average of 3%. Over the past decade, total compensation grew by 29%.

"While many life-sciences companies have downsized at least in some areas, the results of this study show that regulatory professionals are more indispensable than ever," observes RAPS Executive Director Sherry Keramidas, Ph.D. "They play key roles in all aspects of bringing medical innovations to market, and combine strong expertise in medical science, regulation, business, and strategy."

Regulatory experience is a key factor in compensation, according to the data, but the overwhelming majority of regulatory professionals began their careers in another, related field, such as research and development, quality, or laboratory sciences. On average, respondents had eight years of prior professional experience before moving into regulatory, and about 90% hold a university degree in the sciences, a clinical discipline, or engineering.

The work of regulatory professionals has evolved over the past decades and has shifted from an emphasis on compliance to a more varied scope of practice that includes involvement in the full product life cycle from product development through submission, manufacturing, and postapproval, including business and regulatory strategy. The work of regulatory professionals continues to be global and covers many product types, including pharmaceuticals, medical devices, biotech products, and others.

**DR. SHERRY KERAMIDAS**
*RAPS*

*"There is strong demand for qualified regulatory professionals right now, and RAPS research suggests that many professionals are being recruited to new organizations, underscoring the importance of developing and retaining regulatory talent."*

the importance of developing and retaining regulatory talent."

According to Dr. De Rosch, the multidisciplinary team will need to extend beyond the walls of the pharmaceutical company to all parties involved in the research, development, and manufacture of drugs as partners in the process. He believes regulatory professionals can no longer operate with a local-only mentality; every product and regulatory decision must consider a global perspective.

While larger companies often have global affiliates from which they can collect that sort of intelligence, smaller companies like Inspiration Biopharmaceuticals rely on global regulatory CROs, professional networks, and trade organizations to assist in intelligence gathering, Dr. De Rosch says.

"Information can come from a clinical research associate who visits a clinical site in India that has just been inspected by FDA for a clinical product, or from a trip to a contract manufacturing plant which had just been subjected to an FDA preapproval inspection for another product," he says. "By monitoring how CMOs, CROs, and clinical sites are responding to FDA's global presence, the pharmaceutical industry can gather regulatory intelligence to help plan for the next development candidate, the next clinical program, and/or the next marketing application."

## Risky Business

Now that the FDA has extended its reach worldwide, global alignment with current GMPs and GCPs is paramount, according to Dr. De Rosch.

"Manufacturing and clinical-trial sites that

### Building a Benefit-Risk Framework

The Unified Methodologies for Benefit-Risk Assessment (UMBRA) initiative was established by the Centre for Innovation in Regulatory Science (CIRS) in 2012 with the goal of improving benefit-risk assessments during the drug development and regulatory approval process and increasing the transparency, predictability, and consistency with which benefit-risk assessments are conducted. CIRS was recently selected by PhRMA to further the technical development of the work pioneered by the PhRMA Benefit-Risk Action Team (BRAT) and to broaden input from the scientific community into the evolution of this methodology.

A key milestone was accomplished at CIRS' annual benefit-risk workshop in June, when attendees agreed on the common elements of an overarching, internationally acceptable, standardized benefit-risk framework proposed under UMBRA. This framework is serving as the ongoing basis for discussions around the development of novel, dynamic methodological tools to address the needs of benefit-risk assessment throughout a product's life cycle by diverse stakeholders.

Lawrence Liberti, executive director of CIRS, frames regulatory science as the science of developing new tools, standards, and approaches to inform decision-making pertinent to the quality, safety, efficacy, and effectiveness of medicines.

"Each of CIRS' activities, whether focused on developing frameworks and tools to advance therapeutic product development or related regulatory and reimbursement activities, are grounded in the practical application of this definition to help our stakeholders improve their approaches to value-based decision making," Mr. Liberti says.

# VIEWPOINTS

**KEN PHELPS**
*CEO/President*
*Carmargo Pharmaceutical Services*

### An Academic View

Academic and industry-sponsored studies are published in a wide variety of publications. Under 505(b)(2), an application may be made based solely on peer-reviewed articles and other published literature reports, provided there are consistent results from multiple, credible studies. A significant level of detail is presented including descriptions of statistical plans, analytic methods, and study endpoints; endpoints can be objectively assessed and persuasive results can be achieved, yielding a conclusion of efficacy without post hoc analysis.

**GREG KAIN**
*Manager*
*Integrated Project Management Company*

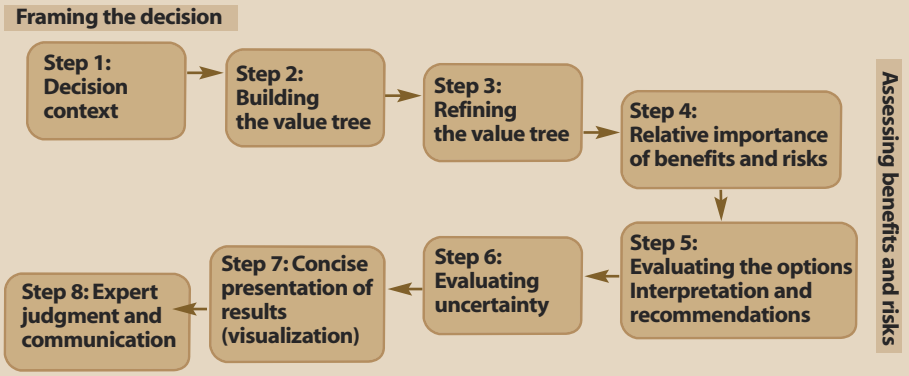
### Process Provides Issue Resolution

Relationship management equals stress management. Compliance issues are often high profile. A lot rides on them. Putting processes in place to solve problems objectively within the internal team keeps tensions down and delivers better results. If there is a dispute between what critical move to make next, it's important to weigh each option according to its risks — impact and probability — which will help cut through ego and emotion and preserve the unity of the team.

### Mapping a Communications Plan

Is there such thing as too much communication? That depends. The last thing you need is for people to be swamped with emails they don't need and waste their time at unnecessary meetings. Mapping out exactly who needs to know what and when, and then codifying it in a formal communications plan, enables team members to remain focused while under the gun.

**Common Elements of the Core UMBRA Benefit-Risk Framework**




Source: CIRS, synopsis from Building the Benefit-Risk Toolbox workshop in June 2012. For more information, visit cirsci.org.

wish to tap into the lucrative U.S. pharmaceutical market must be willing to meet the required FDA inspection requirements or lose credibility with the U.S. pharma industry," he cautions. "This knowledge should make it easier for U.S. companies to approach international manufacturing and clinical trial sites and explain the compliance needs with confidence that these sites will be open to FDA inspection."

Dr. Keramidas says given the different variables depending on the specific product, its intended or approved uses, the supply chain and manufacturing process, and the markets where it is or is intended to be made available, she doesn't think there is one best way to mitigate risk.

"That said, I think companies put themselves in the best position to reduce risk by having the best regulatory teams in place, made up of people with the most up-to-date knowledge, a thorough understanding of the applicable regulations and regulatory issues, and the communications and people skills to work with others in their organizations and at the regulatory authorities to address issues of risk and compliance," she says. "In many ways, it all comes down to having the right people with the right backgrounds and training."

Rather than focusing on risk mitigation, Mr. Lescosky believes companies should focus on creating and implementing the best strategies for successful product development and launch.

"The most effective strategies align team members throughout the organization, effectively training them on their individual roles in the compliance process," he says. "That collaboration and training can allow for better development and launch execution, provide a platform for problem solving, and lower the risk of noncompliance." PV

## EXPERTS

**MARK DE ROSCH, PH.D.** VP, Regulatory Affairs, Inspiration Biopharmaceuticals Inc., a biopharmaceutical company focused solely on serving the hemophilia community. For more information, visit inspirationbio.com.

**SHERRY KERAMIDAS, PH.D.** Executive Director, Regulatory Affairs Professionals Society, a global organization of and for those involved with the regulation of healthcare and related products, including medical devices, pharmaceuticals, biologics, and nutritional products. For more information, visit raps.org.

**LEN LESCOSKY, J.D.** Divisional VP, Chemistry, Manufacturing & Controls, Regulatory Affairs, Pharmaceutical Products Group, Abbott Laboratories, a global, broad-based healthcare company devoted to discovering new medicines, new technologies, and new ways to manage health. For more information, visit abbott.com.

**LAWRENCE LIBERTI.** Executive Director, CIRS — Centre for Innovation in Regulatory Science Ltd., a think tank through which the international pharma industry, regulatory authorities, and academia meet, debate, and develop regulatory and HTA policy. For more information, visit cirsci.org.