Denise Myshko

Evolving Regulations in a Globalized Industry

Global production of FDA-regulated products has quadrupled over the last decade. Regulators and companies have to keep pace with a changing global industry.

Pharmaceutical development and manufacturing have become global industries. But globalization has put many pressures on both industry and regulators to keep pace. Manufacturing, packaging, distribution, and clinical trials are becoming more complex as companies seek out contract organizations to set up both trials and manufacturing throughout the globe.

About 40% of finished drugs come from outside the United States, and 80% of the active pharmaceutical ingredients in medications sold here are manufactured elsewhere. Many of these countries have regulations that are different from the U.S. Food and Drug Administration. Certainly, the International Conference on Harmonization has made progress in developing guidelines, but more needs to be done both at the company and regulatory levels to manage this complex process.

Brad Dawson, managing director, life sciences, at Huron Consulting Group, says pharmaceutical companies will need to have an enterprise-level quality management system that spans geographies to manage the global complexities of drug development.

"In many instances, companies have siloed operations," he says. "A company may have manufacturing operations in Asia and South America, each of which has its own reporting structure and regulatory guidances. We advise clients to take an enterprise view and start to create a holistic approach to make changes. We also suggest that companies have a quality management system with policies and procedures, a robust and active vendor management program, and processes to conduct quality audits in each country on a risk-based approach to identify and self-correct any problems."

David Rosen, co-chair of the life-sciences industry team at Foley & Lardner, who was also formerly with the FDA, says companies need to have a coordinated strategy throughout the world to make sure they have a quality system that is robust.

"This strategy has to ensure that (1) there is appropriate testing and control throughout the manufacturing and product life cycle; (2) staff members continue to be trained on a regular basis; (3) modifications and change controls need to be well-monitored; (4) product complaints and adverse events need to be investigated and trended; and (5) appropriate actions are taken when necessary," he says.

Harmonization of global regulatory operations is key for a cost-effective and efficient pharmaceutical supply chain, says Mahesh Padval, VP, preclinical development and CMC at Verastem, a biopharmaceutical company.

"To manufacture globally acceptable products, companies need to build a worldwide regulatory strategy that starts early in the drug development process and that meets the demands from clinical development to commercial launch," he says. "At Verastem, we are laying the foundation for this by incorporating strategies that take into account regulatory requirements across North America, the European Union, and the Asia-Pacific region."

Many pharma companies already comply with GMPs that are fairly universal, although one global regulation strategy simply won't address the unique needs of each nation, says Ash Kuchel, global group president of Publicis Healthcare Communications Group.

"Consider, for instance, traditional Chinese medicine, which increased in market size from $6 billion to $13 billion from 2006 to 2011, showing a regional commitment to custom and culture in the face of newer, innovative medications," he says. "For this reason, global regulatory bodies should continue to enter into detailed one-on-one GMP contracts tailored to meet national needs versus trying to force-fit one regulatory strategy."

Mr. Dawson says companies are moving toward consistent approaches to how they conduct business, especially in the cGMP space.

"My advice is to have a standard global approach that takes into account all of the requirements and use that as a mechanism for ensuring consistent execution," he says.

John Lindner, VP of the life-sciences practice group at Hitachi Consulting, says companies have to go even further; they need to have a coordinated global network to optimize the costs and the agility of the portfolio instead of focusing on a single set of products or geographies.

"Companies have to look across the entire value chain and across business units end to end — from Phase III clinical trials through scale up and ultimately full-blown commer-

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>
> **BRAD DAWSON** / Huron Consulting Group

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>
> **DR. MAHESH PADVAL** / Verastem

cialization production — to optimize their overall global footprint," he says. "We've seen clients either optimize to a specific set of conditions, a specific set of geographies, or a specific set of cost controls. What we suggest — and it's more work and a lot harder — is to look at all of the variables beyond just the regulatory or the cost constraints to determine where a product fits into the therapeutic portfolio and how that therapeutic portfolio will grow and be managed around the globe. Then life-sciences companies should model and build a network of manufacturing capabilities, both internally and outsourced, which can respond to the global patient needs. An agile network is able to flex and produce products to changing market conditions with complementary and potentially overlapping capabilities."

Mr. Lindner says manufacturing capabilities designed this way allow for more flexibility and lower overall total system costs. He says it's important to optimize global operations across all areas, including regulatory, distribution, product, and commercial issues.

"A global network should be designed not just around regulatory compliance but around all of these areas," he says. "We find inventory-carrying costs go down and that improves cash flow. Flexibility drives responsiveness and, if configured the right way, can become a competitive advantage when launching products into new markets and geographies. A more flexible global network configured against multiple regulatory frameworks in multiple markets allows manufacturers to move new products into the pipeline more quickly."

Mr. Lindner says creating this global network requires a holistic strategy coupled with a deliberate path to drive value, one that assesses overall manufacturing capability inside regulatory compliance frameworks and the growth drivers of the commercial portfolio. It requires a deep set of analytical skills and modeling capabilities to understand how products are going to be launched and distributed and how new products in the portfolio are going to be acquired and assimilated. It's a complicated, multi-variable analysis that needs ongoing evaluation and fine tuning. It is not a one-time exercise.

"This means company executives create a view toward overall capacity, quality, compliance, production planning, inventory planning, and distribution cycles while ensuring that there is a common set of processes, controls, nomenclature, and operating standards that organizations and leaders are reporting and being measured against," he says.

Then, Mr. Lindner says, local or regional teams inside the company can determine how each plant or country-based unit builds its own individual capacity for planning and modeling to incorporate new products, product variations and new customers into the mix.

"But this is all executed under a common operating model that allows manufacturers to ramp up and adjust capacity more rapidly, while ensuring compliance processes are in sync between countries and between sites," he says.

David Elder, VP, technical at Parexel International and formerly with the FDA, says, while a global strategy could help companies address challenges, it is not necessarily viable.

"It is important to recognize that the world is made up of more than 200 different countries, many of which have their own health authorities, different legal frameworks, different areas of expertise, and different degrees of maturity of the regulatory system," he says.

Mr. Elder says the ICH's effort in the area of drug regulations is a model of collaboration among many health authorities with input from the regulated industry and is an example of attempts to devise standards.

"This represents a good effort and it is leading to a more harmonized industry in both the practices that the industry employs and the regulation of the industry by the health authorities," he says.

FDA's Global Efforts

A few years ago, the FDA began an effort to create a more global regulatory agency. Over the next decade, regulators say the agency will continue to transform from a U.S.-focused organization to one that can address FDA-regulated products in a globalized economy. FDA officials say they are using a variety of strategies to get there, including partnering with other regulatory agencies and organizations, strengthening global capacity, developing and harmonizing science-based standards, and analyzing information and data globally.

This effort goes across the entire spectrum

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> **ASH KUCHEL**
> Publicis Healthcare Communications Group

of products the FDA regulates. Specifically in the pharmaceuticals arena, the FDA is establishing international offices and posts to work in partnership with other agencies and provide a platform for inspection of foreign facilities. Regulators are developing risk-based monitoring and inspection strategies and tools that take advantage of developments in science, engineering, and information technology. They are increasing global surveillance and advancing regulatory science.

So far, the FDA has established a permanent in-country presence in China, India, Europe, Latin America, the Middle East, and North Africa and Sub-Saharan Africa. Additionally, in December 2011 the FDA began a program with the EMA to enhance GMP inspection cooperation. The FDA and the European Regulatory Network are working together to share information to meet inspectional obligations.

Until about 15 years ago, drug manufacturing, especially of API, was done in the United States, says Duu-Gong Wu, Ph.D., director with regulatory affairs group, at PPD and a former FDA staff member in CDER.

"Now, 80% of the active pharmaceutical ingredients used in drug manufacturing in the United States come from outside the United States," he says. "The major countries are China, India, and Europe. And that presents a problem with the FDA because often the local GMP regulations and practices are different."

GMP relies on manufacturers themselves to follow the standards based on laws and regulations, Dr. Wu says.

"In the United States, the FDA generally trusts companies to follow the GMP regulations and during inspections, the FDA will look at processes and make a decision on whether there are problems and GMP violations," he says. "That practice may work in the United States, but sometimes it doesn't work in other countries because of differences in cultures and understanding of the concepts of GMP. And the FDA faces limited resources for inspections of all facilities around the world."

Dr. Wu says the agency has tried to expand control by setting up offices in countries such as China and India and relying on collaboration through memoranda of understanding with the regulatory authorities of different countries.

"By this connectivity, the FDA is hoping to be able to bring facilities to higher GMP standards," he says. "The agency has also worked with the WHO and PIC/S, which is a nonprofit organization developing GMP standards. More than 40 international agencies are members of this organization, which has already published a GMP standard. Through these activities and collaboration with international organizations and regulatory authorities, the FDA is trying to bring up the international standard for GMP."

As the industry as a whole moves to a transcontinental discovery, manufacturing, and delivery system, regulatory bodies like the FDA must continue to work across borders to ensure the safety of products, Mr. Kuchel says.

"The FDA is already closely involved in the global trials and manufacturing process, which includes inspections, through international quality standard agreements," Mr. Kuchel says. "Generally, GMP inspections are carried out through national or local agencies. As such, the FDA should more closely align or formalize customized agreements with companies that export product to the United States through formalized QC agreements and increased, proactive communication."

While at the agency, Mr. Elder worked within the FDA's foreign inspection program. He says the agency does more inspections outside of the United States than any other health authority does outside their own countries.

"The FDA conducted more inspections last year than ever before in the history of the agency," he says. "They exceeded 2,500 foreign inspections. The FDA has taken a leadership role in developing a global strategy that involves other health authorities, but its implementation power, obviously, is limited to the United States."

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>
> **DAVID ELDER** / Parexel

Mr. Elder says full execution of the FDA's strategy requires the participation of many authorities as well as the regulated industry.

"Part of the elements of its strategy was to first open foreign offices and leverage the capacity that the agency brings, not just in assisting in the volume of inspections that are done in China and India but also the relationships regulators are building in other countries with the other health authorities to gather technical assistance," he says. "The FDA has made quite a bit of progress, and the foreign offices are a success. The volume of foreign inspections is better, the path toward harmonization is increasing, and there is the new legislation that provides a better legal framework for FDA to do the things it needs to do."

Dr. Padval says based on FDA's limited budget and resources it would be challenging in the current environment for regulators to have complete oversight over global manufacturing and global trials.

"It is important for them to continue working with other agencies globally," he says. "This will harmonize policies and procedures so that oversight or audit by local or other authorities provides a sufficient product safety net worldwide. Even though this may not be possible to implement globally, it would at least allow them to allocate their resources to selected regions of the globe based on risk."

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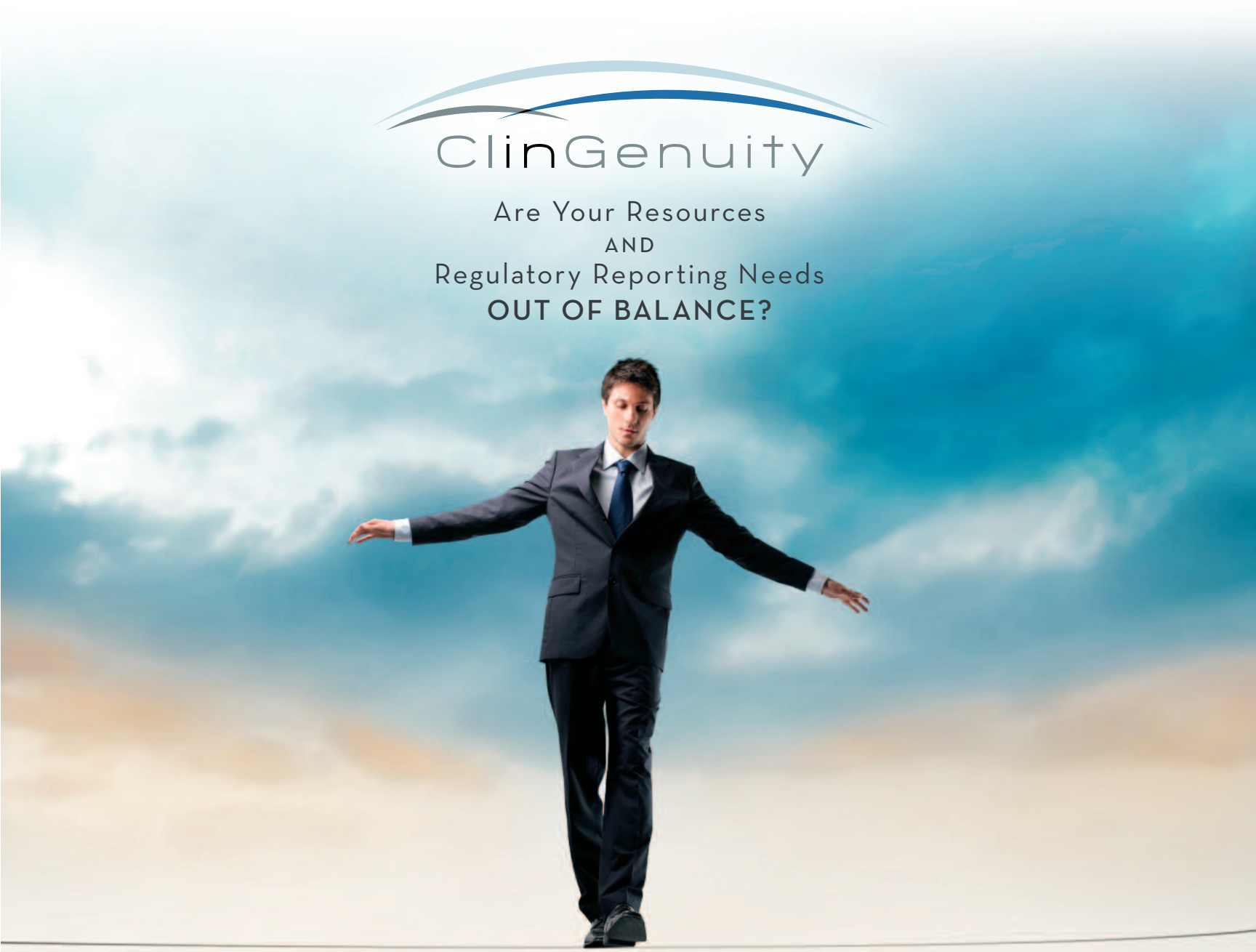

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Mr. Dawson says the agency's oversight is a function of funding and having the ability to get resources where they are needed.

"The FDA wants to be in the field and collaborate with local regulatory authorities to ensure that production not only meets GXP requirements but also aligns with international standards," he says.

The real issue, Mr. Dawson says, is for manufacturers and sponsors to adhere to global regulations and to put processes in place to ensure that they are following GCPs, cGMPs, local regulations, and international standards for those countries in which they will have marketing authorization.

"The FDA is a watchdog agency and it can't be in all places all the time," he says "Regulators are collaborating with different global entities so that they can share data. There is a tremendous push within the FDA to enhance its technologies so that it can identify risks, including repeat offenses. The aim is to enhance collaboration and share this information with other health regulatory bodies, so that FDA can leverage the entire global regulatory community to ensure the safety of the drug supply."

On the clinical trials side, the agency must play an ever-increasing role to keep up with the growing number of clinical trials being done overseas, says James Kewley, principal consultant, at Parexel and formerly with the FDA.

"Global trials are increasing by leaps and bounds, but the FDA's resources are not expanding by leaps and bounds so it's certainly a challenge to perform a rising number of inspections," he says. "Those inspections are much more costly for the FDA to perform than domestic inspections so resources have to keep climbing just to stay even."

Mr. Kewley says FDA's foreign offices need to be more fully staffed.

"My perspective is the FDA needs more boots on the ground," he says. "The reauthorization of PDUFA V will be a big help for ensuring funding for a number of years. The more visibility the FDA has the more things will improve."

Meeting Standards

Experts say it's important to work with regulators early in the process and embrace the concepts of good manufacturing practices.

"If companies are going to work in the highly regulated space of producing pharmaceutical or medical devices, they have to have in place the infrastructure, the training, and experience in process and finished product controls, which are necessary to produce products that meet the appropriate standard of identity, strength, quality, purity throughout the product life cycle," Mr. Rosen says. "Companies have to devote the resources — personnel, fiscal, and capital expenditures — to continue to upgrade, modernize, and put procedures in place to make sure they continue to comply with good manufacturing practices and quality systems requirements. They have to be committed from the top down and the bottom up."

Mr. Lindner says companies have to more proactively solicit input from agencies.

"Companies have to understand the implications of setting up manufacturing in, for example, eastern Europe, India, or parts of Russia and the implications of moving those products out of those trade zones into other parts of the world," he says. "This is a discussion not just with regulators about drug safety and efficacy with the likes of Ministries of Health or FDA, but may also include discussions with Customs and Border Protection, the Drug Enforcement Agency for controlled substances, etc. It involves proactive discussions with all of those involved in trade and customs."

Additionally, industry experts say it's important to make sure partners and suppliers also are complying with regulations.

Dr. Padval says companies can ensure that their global suppliers meet cGMP requirements by selecting vendors that in the recent past have successfully passed audits by multiple global regulatory agencies.

"This should give a company reasonable assurance that their cGMP system and procedures have been looked at from different angles and are in compliance," he says. "It is also important to conduct a technical/quality audit for the specific project under consideration to make sure it can be conducted under the current cGMP systems in place."

Industry leaders stress it's important that companies audit suppliers and partners, including CROs, CMOs, and contract manufacturing organizations.

"In the past, U.S. pharmaceutical companies may have assumed their suppliers would follow standards and would only do an audit occasionally before getting supplies," Dr. Wu says. "But with different cultures and different business practices, that may not be enough to assure the product quality, based on the recent case of heparin and melamine contaminations."

Mr. Dawson recommends companies have an effective vendor management plan in place.

"For manufacturers, this means conducting a quality compliance audit of suppliers and sometimes going to your suppliers' suppliers to assess raw materials and risk ensure and risk that the excipient ingredients or the precursors are coming from a facility that is also following cGMPs. It's not enough to look at your primary vendor and accept the certificate of analysis. It is important to understand your vendor's quality management system, including their training program to minimize compliance vulnerabilities so that when product comes into your system, you have a high degree of confidence that it is safe and efficacious." PV

FDA's Global Focus

- About 40% of finished drugs come from overseas, and 80% of the active pharmaceutical ingredients in medications sold in the United States are manufactured elsewhere. Half of all medical devices used in this country are imported.
- Just a decade ago, 6 million shipments of FDA-regulated goods passed through the nation's 300 ports of entry. In 2001, that quadrupled to 24 million shipments. Each year over the last seven years, imports of pharmaceutical products have increased at almost 13% and devices have grown at more than 10%.
- FDA inspections of overseas drug manufacturing plants increased from 333 in 2007 to 424 in 2009.
- The FDA has collaborated with its counterparts in Australia on drug inspections, engaged in harmonization of drug regulation via the International Conference on Harmonization, and joined the Pharmaceutical Inspection Cooperation/Scheme (PIC/S), which is an informal organization of the drug manufacturing inspectors from 39 countries.
- The FDA does not — nor will it — have the resources to adequately keep pace with the pressures of globalization. In 2008 the Government Accountability Office recommended that the FDA increase inspections of foreign drug establishments and improve information it receives to manage overseas inspections. But at current rates, it would take an estimated nine years for the FDA to inspect every high-priority pharmaceutical facility just once.

Source: Food and Drug Administration

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