Denise Myshko

Compliance with GCP

With more clinical trials being done outside the United States and an increased focus by regulators on patient safety, it's critical for pharma companies to follow good clinical practices in their development programs.

Regulators around the globe are requiring more data from pharmaceutical companies as part of their applications for new drugs. This, coupled with an increased focus on patient safety, is creating an environment that requires companies to be up to date on current regulations and guidelines issued by multiple regulatory authorities.

Noncompliance with current regulatory guidelines can put patients at risk, delay product launch, and even result in fines. An effective clinical compliance program can help achieve timely, efficient, and safe clinical trials that conform to GCP regulations.

Good clinical practices are about two things: the protection of human subjects and ensuring the data are good, says Bill Greenrose, a director in the governance, regulatory and risk strategies practice, at Deloitte & Touche.

"Protection of human subjects is the most important point from the FDA's perspective," he says. "The agency wants to make sure people don't get hurt unnecessarily but regulators also want to know if the protocol achieves a measurable objective endpoint. This is about making sure all the data are collected properly in support of a product."

The global environment of clinical research requires companies to be vigilant about keeping up with current regulations, Mr. Greenrose says.

"People latched on to the idea that doing studies outside the United States was faster, better, and cheaper," he says. "Properly set up with the right input from the FDA, they can be. But companies should have a collaborative relationship with the FDA; they can't operate in a vacuum."

Furthermore, he points out that regulations are not static in any country.

"Companies need to stay on top of the requirements," he says. "Regulations are dynamic in every country, and they are evolving rapidly. In addition to any potential fines or penalties, the product could be removed from the marketplace."

Mr. Greenrose says he finds that companies — especially if they are located outside the United States — may lack knowledge of the specifics of the U.S. marketplace.

"For these companies, at the corporate level, there is a lot of pressure to get products through the development cycle yet at the individual level, many outside the U.S. not involved in the R&D process lack understanding of the U.S. regulations at the micro level," he says.

This pressure on R&D to accelerate the timeline is partly what led many to conduct trials outside the United States.

"Some companies may think that conforming to International Conference on Harmonisation (ICH) guidelines will be enough to address regulators' concerns," he says. "But ICH can't standardize everything because the laws are different country by country. The challenge is that individual countries still have idiosyncratic issues that must be addressed."

Debbie Thomas, VP of global regulatory affairs, West Pharmaceutical Services, says another challenge that companies face is the sheer volume of regulations on a global scale.

"Agencies have become much clearer in defining their expectations and their requirements, but the volume of global regulations and guidances has grown significantly," she says. "There is also a shorter comment timeframe for draft guidances. We all know how difficult it is to balance resources in an ever-changing and evolving environment."

Creating standard operating procedures (SOPs) and conducting regulatory intelligence are the two most expensive and time-consuming responsibilities of a pharmaceutical compliance team, according to a new study by Cutting Edge Information.

Among the drug manufacturers that Cutting Edge Information surveyed for its study, creating SOPs occupies the largest percentage of compliance teams' time and budget, at 16% and 19%, respectively. One reason SOPs take so much time is that compliance teams must bring in human resources from disparate parts of the organization to help write them. For example, SOPs for commercial activities require the compliance team to access marketing ex-

What is GCP?

Good clinical practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with GCP assures that the rights, safety, and well-being of trial subjects are protected and that clinical trial data are credible.

Source: PwC

> **"Regulatory agencies have become much clearer in defining their expectations and their requirements, but the volume of global regulations and guidances has grown significantly."**
>
> **DEBBIE THOMAS** / West Pharmaceutical Services

> **"The industry is spending too much time and effort trying to look at every piece of data. Companies have to step back to see how data come together and then manage from that perspective."**
>
> **SANDY KENNEDY** / Quintiles

perts. The same is true for manufacturing, clinical development, and medical affairs SOPs.

The related documentation review of standard operating procedures accounts for another 5% of time and 7% of budgets. The study also found that internal and external auditing combine to account for about one-tenth of compliance teams' time and budgets. Auditing allows compliance teams to learn whether employees and departments are properly following regulations and implementing SOPs.

Recent Guidances

One important recent FDA guidance, Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, was issued in December that addresses "enrichment strategies" that can be used in clinical trials intended to support effectiveness and safety claims in new drug applications and biologics license applications.

"The FDA has witnessed problems with submissions that delay or derail the approval of medical products," Mr. Greenrose says. "Regulators put this guidance document in place to help clarify what they expect from submissions; it's almost a primer on how to conduct clinical trials."

This guidance points to three areas that can help companies better meet their endpoints: narrowing patient selection criteria to decrease variability to get a better outcome; choosing patients who are more likely to have an endpoint relevant to the disease; and choosing patients who are more likely to respond to the drug, including the use of genetic markers.

"The challenge is that the more restricted the patient population is the smaller the patient pool is and the longer it can take to enroll patients in the study," Mr. Greenrose says. "This is a classic balancing act between trying to ensure a faster, more effective outcome strategy vs. taking a longer road and having a higher probability of success. Every company has a different focus depending on a number of factors, including how big the pipeline is, how much of a need there is for the next successful product, etc."

Sandy Kennedy, senior VP of global quality assurance, at Quintiles, says another important guidance recently issued relates to a risk-based approach to monitoring clinical trials. Both the FDA and the EMA have issued guidances on this topic.

"Traditionally, for industry-sponsored clinical trials, we monitor and send representatives from the sponsor companies to our clinical trial sites to review all of the source medical records against the information in the data that's being submitted for analysis," she says. "It is a very detailed one-to-one review of everything in that medical record."

Technology, Ms. Kennedy says, can now help sponsors and CROs more accurately capture and review source data.

"We use the information platform Quintiles Infosario, which allows us to see within the investigator sites what the commonalities or differences are in the data, the enrollment rate, the adverse event rate, and the drop-out rate," she says. "We're able to identify anomalies and then target our resources to go to a particular site to see what is driving some of these differences. It's a way to identify and target resources to ensure the integrity and quality of the data coming back. The FDA is a strong proponent of this risk-based approach to monitoring of clinical trials. Dr. Janet Woodcock, in particular, has spoken about this at almost every podium opportunity for years to say that the industry is spending too much time and effort monitoring resources and trying to look at every piece of data. Rather, we must utilize the aggregate data."

Ms. Kennedy says companies have to be data-driven to get to the insights that lead to true information-driven, risk-based monitoring of clinical trials.

Best Practices

Mr. Greenrose says one of the most important things that companies can do is maintain an open line of communication and dialogue with regulatory agencies in the local markets in which they plan to get approvals.

"By having a relationship with the regulatory agency, if a problem crops up, companies are a step ahead at facilitating discussions with the regulatory entity early on," he says. "Companies that present their plans and the logic behind the strategy, as well as the risks and benefits, and ask for recommendations will likely have much more productive dialogues with regulators."

Mr. Greenrose points out that companies have to make sure their business partners are meeting local regulatory requirements as well.

"Clinical trials generate data, and data are part of the supply chain," he says. "For years, the industry had this view that clinical was a separate universe. It was the purview of the clinical teams. Then over time, as trials became bigger and more complicated, CROs were brought in to help manage clinical trials. But pharma companies still need to do the proper due diligence and oversight of their partners and their supply chain on the front end of the product life cycle."

Ms. Kennedy and Ms. Thomas both say an important best practice is to train employees on global GCP/GMP requirements. Both of their companies make training mandatory for all employees — including those who are not directly involved in clinical trials or manufacturing — with a test for proficiency.

"A key to effective training is an overarching corporate culture that continually stresses the importance of compliance in a highly regulated industry," Ms. Thomas says. PV

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Denise Myshko

Selected Recent FDA Guidances

From e-submissions to safety, new guidances and regulations continue to redefine the regulatory landscape.

Clinical complexity is creating an environment that requires companies to keep current on regulations and guidelines issued by multiple regulatory authorities. Below is a selection of recent actions taken by the FDA.

Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications, January 2013

This draft guidance provides the requirements for a valid electronic submission.

For more information, visit fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf

Safety Reporting Requirements for INDs and BA/BE Studies, December 2012

This guidance is intended to help sponsors and investigators comply with the requirements for investigational new drug (IND) safety reporting and safety reporting for bioavailability (BA) and bioequivalence (BE) studies.

For more information, visit fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

Providing Submissions in Electronic Format — Summary Level Clinical Site Data for CDER's Inspection Planning, December 2012

This draft guidance addresses the submission of a clinical dataset and describes and summarizes the characteristics and outcomes of clinical investigations at the level of the individual study site.

For more information, visit fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

Safety Considerations for Product Design to Minimize Medication Errors, December 2012

This draft guidance is a set of principles for developing drug products using a systems approach to minimize medication errors relating to product design, and is the first in a series of three planned guidances to minimize risks contributing to medication errors.

For more information, visit fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs, December 2012

This guidance summarizes the investigational new drug application (IND) process for unapproved positron emission tomography (PET) drugs, makes recommendations on how to submit an IND, and provides advice on investigational PET drug access option.

For more information, visit fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291573.pdf

Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products, December 2012

This draft guidance discusses enrichment strategies that can be used in clinical trials intended to support effectiveness and safety claims in new drug applications (NDAs) and biologics license applications (BLAs).

For more information, visit fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf

ICH Q11 Development and Manufacture of Drug Substances, November 2011

This guidance looks at the aspects of development and manufacture that pertain to drug substance, including the presence of steps designed to reduce impurities. In addition, this guidance provides further clarification on the principles and concepts described in certain ICH guidances.

For more information, visit fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf

Electronic Source Data in Clinical Investigations, November 2012

This draft guidance provides recommendations for those involved in capturing, reviewing, and archiving electronic source data in FDA-regulated clinical investigations.

For more information, visit fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf PV

Annual Meetings You Cannot Afford to Miss

Marketing Pharmaceuticals 2013

GRAND HYATT WASHINGTON
WASHINGTON, DC

Tutorial: February 19
Workshop: February 20-21

At this workshop you will learn from experts the best ways of conducting marketing in a highly regulated environment. Hear from the FDA directly on evidence requirements, underlying issues with health economic analyses, enforcement actions, and even social media.

Visit **diahome.org/MarketingPharma2013** for the full agenda.

Medical and Scientific Communications 2013 Annual Forum

SHERATON WILD HORSE PASS RESORT & SPA
CHANDLER, AZ

Core Curriculum & Tutorials: March 18
Forum: March 19-21

This multi-track forum will give insight into the intricacies of Medical and Scientific Communications. The content of this year's forum has been expanded and reorganized to better serve health care professionals involved in the Medical Communications, Medical Writing, and Medical Science Liaison functional areas.

Visit **diahome.org/MSC2013** for the full agenda.

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