Life & Health

Clinical Communiqué

Q3 2013

KEEPING AN EYE ON CHINA

Already a powerhouse of API and generics manufacturing, China is staking its claim as a global center for clinical research and drug development thanks to aggressive investment by the Chinese government and multinational Life Science companies. China is committed to expanding its Pharmaceutical sector, both domestically and through international investment. According to Lux Research, the government's R&D investment has reached a cumulative $160 billion. For their part, many of the world's leading Pharmaceutical companies – Novo Nordisk, AstraZeneca, GlaxoSmithKline, Merck and Novartis to name a few – have invested hundreds of millions of dollars in clinical research and drug development operations in China.

It's hard to argue with the opportunities for clinical research in China; massive innovation centers and "super complexes" supported by the Chinese government, a pool of hundreds of millions of potential study participants, and a growing body of top-quality research scientists. Notwithstanding those attributes, China continued to struggle with a reputation for corruption, questionable product quality and lax regulatory controls. Now, China is taking on that reputation with new regulations, aggressive scrutiny of the Pharmaceutical industry and no-nonsense enforcement actions. As a result, sponsors of clinical trials are facing a wave of new domestic and international risks.

(continued...)

KEEPING AN EYE ON CHINA *(Continued)*

Data Quality and Corruption

GlaxoSmithKline (GSK) became the symbol of China's newly robust enforcement approach in July when Chinese officials accused the British Pharmaceutical giant of funneling money through small travel agencies to pay nearly half a billion dollars in bribes to doctors, hospitals and government officials. Four GSK executives were detained as the Chinese government pursued its investigation into GSK's alleged wrongdoing. Only a month earlier, GSK fired its head of Chinese Research and Development following discovery that he had misrepresented data in an article written for a medical journal. In GSK's 2012 Annual Report, the company reports that it had been contacted by the US Department of Justice related the the US Foreign Corrupt Practices Act.

While the allegations against GSK highlight the risks in the sales and marketing of drugs in China, pharmaceutical sponsors face multiple and growing risks related to clinical trials conducted in China. A July 14th article by *Bloomberg News* reported on Bristol-Myers Squibb Co. and Pfizer Inc.'s development of the blood thinner Eliquis. According to the Bloomberg report, approval of the drug was stalled for nine months because of "...misconduct, errors and an alleged cover-up attempt at a Chinese trial site..." FDA documents cited by Bloomberg say the delay came after the company disclosed that patients received the wrong medicine, serious adverse events went unreported and records were changed. As a result, the FDA conducted a lengthy reanalysis of the data that delayed eventual approval and market entry. Consider that the clinical trial for Eliquis included more than 1,000 study sites, with about three dozen located in China, yet the questionable data from China delayed drug approval and sale by nine months.

A July 22nd report in the *New York Times* reinforced the risks during clinical trials in China, focusing on GSK. According to the report, a GSK executive had been advised of problems identified through an internal audit regarding the conduct of research at the company's drug development center in China. According to the confidential audit document obtained by the Times, auditors found multiple problems, concluding that workers "... at the research center did not properly monitor clinical trials and paid hospitals in ways that could be seen as bribery." The Times noted, "The report warned of 'reputational, financial and/or regulatory action risk where payments made to investigators regardless of actual work completed are perceived as bribery or corruption." GSK responded to the article, explaining that they had taken appropriate steps to address the issues identified by the audit and had tightened payment procedures for clinical research coordinators.

While current attention focuses on GSK, Bristol Myer Squibb and Pfizer, all clinical trials in China are likely to come under scrutiny by government officials inside and outside the country. The US Department of Justice and the UK's Serious Fraud Office routinely scrutinize global Pharmaceutical companies for violations of the FCPA and the UK Bribery Act. The US FDA has strengthened its collaboration with its Chinese counterparts to ensure drug safety. In a May 22nd statement before the US Congressional-Executive Commission on China, the FDA's Associate Director for Global Operations and Policy Steven M. Solomon described a series of activities the Agency had undertaken with the China Food and Drug Administration. One activity noted by Solomon deserves special note:

Between 2010 and 2012, the FDA held a series of workshops on good clinical practices for Chinese inspectors of sites that conduct clinical trials. Solomon noted, "Prior to the workshops, CFDA had few well-trained inspectors able to conduct inspections of clinical research sites. The FDA's training in this area helped CFDA to establish its national clinical research inspectorate."

Looking Forward

China's regulatory environment for clinical trials remains in flux. On July 11th, China's Center for Drug Evaluation released a long-term proposal for plans to improve the regulation of clinical trial data. The proposal, which acknowledges the absence of rules and enforcement across multiple jurisdictions, came on the heels of the reports concerning potential misconduct in the China-based trials. The Proposal to Standardize Pharmaceutical Clinical Trial Data Management sets out goals addressing issues including poor standards and inadequate guidance. How the Proposal will play out over the projected 2013-2015 schedule remains uncertain.

Despite the uncertainty of China's long-term plans regarding clinical trial regulation, it is certain that multinational Pharmaceutical companies with clinical, manufacturing or marketing interests in China will be held under intense scrutiny by Chinese government officials and their counterparts in the US.

WHAT BIMO INSPECTIONS REVEAL

The US Food and Drug Administration's (FDA) Bioresearch Monitoring Program (BIMO) has a three-pronged mission:

- To protect the rights, safety and welfare of subjects in FDA-regulated trials;
- To determine the accuracy and reliability of clinical trial data submitted to the FDA in support of research or marketing applications for new products;
- To assess compliance with the FDA's regulations governing the conduct of clinical trials, including those for informed consent, ethical review and control of research articles.

BIMO inspections are assigned by FDA Centers including the Center for Drug Evaluation & Research (CDER), the Center for Devices and Radiological Health (CDRH) and the Center for Biologics Evaluation and Research (CBER). In FY 2012, more than 1,000 inspections were completed, with CDER conducting the largest number and Clinical Investigators (CI) representing the most common inspection group.

In a May 2nd, 2013 presentation Nancy A. Bellamy, Bioresearch Specialist/BIMO Monitor with the FDA's Office of Regulatory Affairs, identified the most common observations for Clinical Investigators during a BIMO inspection:

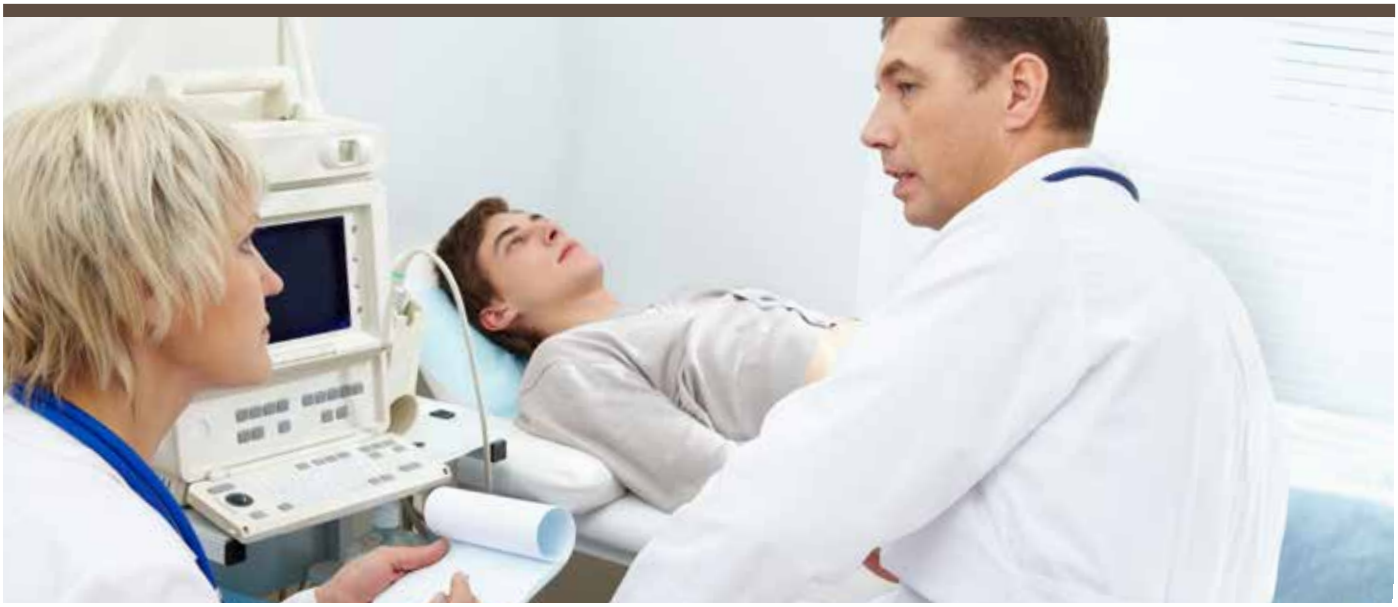
1. Protocol deviations – inclusion/exclusion; schedules – dosing, lab tests, return visits, medications;
2. Failure to report Adverse Events (AEs);
3. Poor recordkeeping, missing source documents;
4. Informed consent issues – including the wrong versions;
5. IRB issues – approvals; reports of Severe Adverse Events (SAEs)/deviations;
6. Test article accountability (a CI responsibility);
7. Failure by CI to adequately supervise the study – i.e., staff errors, training lapses.

With "What's going wrong" as a starting point, Bellamy offered a number of "tips for successful research studies."

Her tips, which reinforce our recommendations to many clinical clients, are worth listing:

- Understand protocol requirements and limitations;
- Train all employees including document handling. We would add that all training must be current and understandable. Given the number of foreign clinical trials, training has to match the culture, language and knowledge levels of the learner;
- Use the latest version of the ICF control documents;
- **Keep all records** including letters, faxes, emails, memos and phone contacts involving sponsors, IRBs, monitors and subjects;
- Keep all test article accountability records (shipping receipts, enrollment logs, dispensing logs);
- Keep complete, organized and adequate records (attributable, legible, contemporaneous, original and accurate);
- Know your IRB's requirements for continuing review, ADEs, amendments and recruitment ads;
- Know the sponsor's Adverse Event reporting requirements;
- Remember that protocol deviations are not protocol revisions;
- Be open about errors, document and report all deviations, and record the sponsor's decisions;
- Know each study staff member's roles and responsibilities;
- Establish and document clear delegation of authority.

Adequate Clinical Investigator and staff knowledge is an obvious, critical element of an effective, defensible and compliant clinical trial. As the complexity of trials and dispersal of study sites (a late-stage clinical trial can have hundreds of study sites across dozens of countries), the delivery and documentation of compliant training has become more important than ever. It is equally important for sponsors, IRBs and Clinical Investigators to remember that the test of effective training is learner knowledge and behavior – not the number of training hours or courses provided.



UNDERSTANDING FDA'S INSPECTION APPROACH

The FDA's BIMO program is a wide-ranging program for ensuring patient safety and data integrity in the conduct of clinical trials. More than 1,000 inspections of study sites were conducted in 2012 (see *FDA's New Guidance Focuses on Risk-Based Monitoring*). Often, site personnel lacked adequate knowledge to understand, implement and monitor applicable FDA regulations.

UL Quality, Compliance and Learning maintains a comprehensive library of courses that enable sponsors, clinical site personnel and monitors to comply with all relevant regulations. Under a unique agreement with the FDA, we also develop courses to train FDA investigators as part of the FDA's ORA U online university. Those same courses are available to the industry, offering a unique perspective into the thinking and training of FDA inspectors. Using the BIMO training program, clinical professionals can become familiar with the FDA's expectations for clinical trials and ensure responsive actions.

Our BIMO Training Program includes the following courses:

- **Introduction**: Overview and historical perspective of FDA's BIMO program;
- **General Inspection Assignment Process**: Overview of the general inspection assignment process, site selection and background materials used in a BIMO inspection;
- **Institutional Review Boards**: Overview of of the regulations applicable to the protection of human subjects participating in clinical research and the role of IRBs in monitoring and managing clinical trials;
- **Clinical Investigator Responsibilities**: Focuses on the responsibilities of a clinical investigator who participates in clinical research involving unapproved test articles under FDA's jurisdiction;
- **Sponsor/Monitor Responsibilities**: Addresses the responsibilities of sponsors, monitors and Contract Research Organizations involved in conducting clinical research;
- **In Vivo Bioequivalence Program Part 1**: Introduction to the In Vivo Bioequivalence Compliance Program, one of seven compliance programs under BIMO;
- **In Vivo Bioequivalence Program Part II**: Covers the challenges of inspecting clinical and analytical facilities.

Our BIMO Training Program is used by the FDA to standardize inspections of clinical trials, helping to ensure a consistent investigational approach across all clinical trials, regardless of their location. For the regulated community, understanding the thinking and expectations of FDA inspectors can streamline the inspection process and improve the efficiency of compliance with applicable FDA regulations.

TRANSFORMING CLINICAL TRIALS

Sponsors and CROs, monitors and clinical personnel agree that consistent, high-quality learning, communication and management systems are essential to protecting participants in clinical trials while accelerating patient access to innovative, effective new drug therapies. Despite that common recognition, clinicians have grappled with unresponsive systems that lacked the education and communication tools to ensure human subject protection, data integrity and regulatory compliance.

The WCG Academy was developed to address gaps in clinical trials knowledge, particularly for those whose roles impact the care of study patients. The WCG is a knowledge portal, providing the most current clinical knowledge related to good clinical practices and research ethics for human research.

What sets the Academy apart is the strength of its collaborative partnership and the resources each partner brings to the table:

- **UL Quality, Compliance and Learning**, formerly EduNeering, is a leader in providing knowledge, compliance and communications solutions to the Life Science community. UL's extensive library of courses and communications tools includes those used by the FDA to train its inspectors and investigators through the agency's online university, ORA U. The FDA's online university operates on UL's cloud-based technology platform, ComplianceWire®, which is already used by more than 300 Life Science companies around the world for training, compliance and communication among dispersed facilities and sites.
- **WIRB-Copernicus Group (WCG)** is the world's largest provider of regulatory and ethical review services for human research. Eight AAHRPP accredited panels, more than 100 experienced board members and over 60 years of combined experience in protocol and study-related review position WIRB-Copernicus Group to provide critically important services to ensure the safety and welfare of research subjects worldwide.

Resolving Traditional Shortcomings

Sponsors and CROs have historically faced hurdles in certifying study sites on study protocol and GCP/IHC before drugs can be shipped and patients can be enrolled at the site. Required training is often disjointed, typically provided by multiple vendors, with effectiveness frequently limited by the language, literacy and understanding of study personnel at widely dispersed sites. Complicating the challenge, study sites are required to have specified training for each study they conduct; as a result, site personnel often take the same courses over and over. Third-party training resources vary in quality and routinely fail to deliver the necessary standard of quality and compliance set by reputable IRBs.

The WCG Academy is a transformational initiative that incorporates training and certification in a one-stop solution that is higher quality, easily customized and integrated into any individual clinical trial, and compatible with other WCG services. The ComplianceWire® platform enables standardized cloud-based training distribution with e-records of completions, regardless of learner location, and is maintained by the IRB across the network of sites. If recent training has been completed by personnel at one site, WCG can waive retraining requirements. Content is drawn from UL's library of FDA-authored, reviewed and used coursework.

The WCG Academy is expected to drive adoption of best practices, improve patient selection and retention, and minimize the risks of site staff turnover or noncompliance. For study participants, the result is better care and safety. For clinical staff personnel, the Academy will provide support in meeting their responsibilities, both ethical and regulatory, to protect the health and safety of their study participants – and to ensure that safe, effective new drugs reach patients as quickly as possible.

FDA'S FINAL GUIDANCE FOCUSES ON RISK-BASED MONITORING

Sponsors of modern clinical trials carry responsibility for the protection of human subjects and the integrity of data from trials that can include hundreds of study sites across dozens of countries. Fulfilling that responsibility requires sponsors to monitor these study sites, clinical investigators and site personnel to ensure that protocols are followed, data is collected and recorded, and study subjects are protected. The growing complexity of clinical trials has complicated that already-difficult function, preventing or postponing the availability of new medical treatments that can improve the lives and health of millions of patients.

The US Food and Drug Administration (FDA) recognizes the difficulty sponsors face in ensuring both human subject safety and data integrity across many study sites. At the same time, the Agency highlights the growing adoption of Electronic Data Capture (EDC) and centralized statistical data analysis as practical, effective tools for monitoring clinical trials. In August 2013, the FDA went a step further with the publication of *Oversight of Clinical Investigations – a Risk-Based Approach to Monitoring*. Even though it does not establish legally enforceable responsibilities, the final Guidance aligns with the goals of ICH E6 and ISO 14155 by specifically providing for "... flexibility in how trials are monitored."

The FDA explains its approach to monitoring in the Guidance, "There is a growing consensus that risk-based approaches to monitoring, focusing on risks to the most critical data elements and processes necessary to achieve study objectives, are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality." The FDA now encourages a greater use of centralized monitoring while also recognizing that on-site monitoring still has a valuable role when indicated by the associated study risks.

According to the FDA Guidance, "Sponsors should prospectively identify critical data and processes that if inaccurate, not performed or performed incorrectly, would threaten the protection of human subjects or the integrity of the study results." Examples of data and processes that should ordinarily be identified as critical include:

- Verification that informed consent was obtained appropriately;
- Adherence to protocol eligibility criteria;
- Procedures for documenting appropriate accountability and administration of the investigational product;
- Conduct and documentation of procedures and assessments related to study endpoints;
- Protocol-required safety assessments;
- Adverse events;
- Conduct and documentation of procedures essential to trial integrity.

"Following the identification of critical data and processes, sponsors should perform a risk assessment to identify and understand the nature, sources and potential causes of risks that could affect the collection of critical data or the performance of critical processes." Identified risks should be assessed and prioritized by considering the likelihood of errors occurring, the impact of such errors on human subject protection and trial integrity, and the extent to which such errors would be detectable.

FDA'S NEW GUIDANCE FOCUSES ON RISK-BASED MONITORING *(Continued)*

"A monitoring plan ordinarily should focus on preventing or mitigating important and likely risks, identified by the risk assessment, to critical data and processes." The FDA recognizes that the monitoring activities will depend, in part, on a range of factors, considered during the risk assessment, specific to the individual clinical investigation. Among those factors: the complexity of the study design, the types of study endpoints, the clinical complexity of the study population, geography, the relative experience of the clinical investigator and of the sponsor with the clinical investigator, the use of electronic data capture, the relative safety of the investigational product, the stage of the study and the quantity of data.

The FDA Guidance goes on to explain five general components that might be included in a monitoring plan:

- A description of the monitoring approaches used;
- Communication of the monitoring results;
- Management of noncompliance;
- Ensuring quality monitoring;
- Monitoring plan amendments.

The FDA suggests that a risk-based approach to monitoring is one component of a multi-factor system for ensuring study quality. The updated FDA Guidance makes note of four additional quality strategies necessary to support a risk-based monitoring plan:

- Well designed and articulated protocol;
- Meaningful clinical investigator training and communication;
- Clearly evaluated and articulated delegation of responsibilities;
- Refined clinical investigator/site selection and initiation.

About UL Quality, Compliance and Learning

UL Quality, Compliance and Learning is a business line within UL Life & Health's Business Unit. UL is a global independent safety science company offering expertise across five key strategic businesses: Life & Health, Product Safety, Environment, Verification Services and Enterprise Services.

UL Quality, Compliance and Learning develops technology-driven solutions to help organizations mitigate risks, improve business performance and establish qualification and training programs through a proprietary, cloud-based platform, ComplianceWire®.

For more than 30 years, UL has served corporate and government customers in the Life Science, Health Care, Energy and Industrial sectors. Our global quality and compliance management approach integrates ComplianceWire, training content and advisory services, enabling clients to align learning strategies with their quality and compliance objectives.

Since 1999, under a unique partnership with the FDA's Office of Regulatory Affairs (ORA), UL Quality, Compliance and Learning has provided the online training, documentation tracking and 21 CFR Part 11-validated platform for ORA-U, the FDA's virtual university. Additionally, UL maintains exclusive partnerships with leading regulatory and industry trade organizations, including AdvaMed, the Drug Information Association, the Personal Care Products Council, and the Duke Clinical Research Institute.