Drug Companies Face Stricter Clinical Trial Regulation Worldwide

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For the better part of a decade, drug and medical device companies have shipped a growing percentage of their clinical trials for new drugs and medical devices to foreign nations. A new wave of regulation, however, much of it aimed at protecting test subjects and assuring the integrity of data, is presenting new compliance challenges and changes to how those studies are conducted at home and abroad.

With large populations, a low-cost of doing business, and a huge potential marketplace, countries like China and India have attracted an increasing share of clinical trials. “It's a question of economics. It is simply cheaper to do your trials overseas and that's driving more and more folks to push their trials,” says Matthew Weinberg, CEO of The Weinberg Group, the nation's largest independent auditor of clinical trials. Even those traditionally business-friendly environments, however, are taking a fresh look at how trials are conducted. Regulations in the United States and European Union are also becoming more stringent and some countries want more controls on clinical trials done abroad if manufacturers want to sell into their markets.

While there remain economic advantages to moving clinical trials abroad—“the benefits outweigh risks at least for the moment,” Weinberg says—human rights advocates warn of the potential abuse of test subjects, a concern at the core of new regulations.

“The goal of many regulations pertaining to clinical trials is ensuring the safety of the test subjects,” says Tristan Gabriel, senior vice president of ACE Life Sciences' medical risk group. “That's the underlying theme in many regulations promulgated by such agencies as the US Food and Drug Administration and the European Medicines Agency.”

“Clinical trials are a critical component in a company's gaining necessary approvals to sell their product in a particular country,” he adds. “A clinical trial must be run in the right way from a compliance perspective. Is it is not, local authorities may reject the trial's finding and require the sponsor to redo the entire study. If a sponsor encounters a situation where its product cannot be sold in a particular country, or if it must re-run its clinical trial, it can cost millions of dollars in upfront costs and lost revenue and profits.”

India Wants Video Evidence

India, by nature of its massive population, is a hub of clinical trial activity and among the most active-countries lately to adopt new regulations on how clinical trials are conducted. New trial
rules for drug and cosmetic companies issued in December, for example, require an audio or video recording of the informed consent process in all trials.

“The new requirement is likely to create procedural inconvenience for Investigators apart from increasing the cost of conducting clinical trials,” wrote Anay Shukla and Khushboo Baxi, partners with the international law firm Nishith Desai Associates, in a recent client advisory. “Since the order does not specify any details on preservation of the records, it is unclear on what the minimum duration is for which the recordings have to be preserved. In addition, since collection and storage of sensitive personal data or information in the audio-visual recording will be in electronic form, requirements for compliance with the Indian data protection laws will also be a necessity.”

Another change is that drug and medical device companies that sponsor trials must disclose financial information in their contract with the organization that administers the trial, known in the industry as the investigator. This includes financial support, fees, honorarium, and payments-in-kind paid to the investigator at the time permission to conduct clinical trials in India was sought.

China Concerns

China, also a popular destination for clinical trials due to its large population and low-cost labor supply, is also strengthening its oversight. It recently told companies they will have to register with the World Health Organization's international clinical trials registry platform and maintain data in accordance with the WHO's policies.

A concern for companies conducting studies in China is how the FDA will view the data. Last year, Bristol-Myers Squibb and Pfizer had the approval of the blood thinner Eliquis delayed for several months in the United States over concerns of erroneous and falsified data, dosing errors, and unreported incidents at the drug's Chinese trial site.

European Union Seeks Harmonization

The European Union is a challenging marketplace for drug and device trials because each member state can impose its own rules and standards. That could be about to change, as the European Parliament seeks to repeal its current clinical trial directive and adopt revised rules that supersede those in member states. A rule proposal released in December sets requirements that must be enacted by member states and, for the first time, clinical trials would be held to uniform standards across Europe.

“The goal for a lot of these regulations is patient safety. That's the underlying theme for many of them, including the U.S. Food and Drug Administration and the European Medicines Agency.”

—Tristan Gabriel,
SVP, Medical Risk Group,
ACE Life Sciences
The proposed regulation would require sponsors to submit their application to a new European Medicines Agency Web portal used by all member states. Approval criteria will include participant and trial site suitability and how compensation will be awarded in the event of death or injury. New rules applying to the suitability of patients establish tougher restrictions on the use of minors, the incapacitated, and pregnant women.

**U.S. Agencies Consider New Rules**

Regulators in the United States are also considering potential changes to how they review trials. The Department of Health and Human Services, for example, is currently working on revising its existing regulations, as signaled in a recent Notice of Advanced Rulemaking. New rules would cover how subjects give informed consent and are protected throughout the process, and they would add new registration and transparency requirements.

The Food and Drug Administration is also taking a fresh look. Among its concerns, which could influence rulemaking, are that trials should do a better job including those with chronic conditions, such as heart disease and diabetes. An internal memo the agency issued in January, urged that “at least one trial in a broad population that closely resembles the people who will use the drug if it is approved, and should discourage unnecessary exclusions.” Drug companies traditionally have excluded those with chronic medical conditions, when possible, fearing they could present complications that muddy data and slow the approval process.

**A RISK-BASED SIDEBAR**

**The following is from guidance issued by the Food and Drug Administration on the oversight of clinical investigations and a risk-based approach to monitoring trials.**

During the past two decades, the number and complexity of clinical trials have grown dramatically. These changes create new challenges to clinical trial oversight, particularly increased variability in clinical investigator experience, site infrastructure, treatment choices, and standards of health care, as well as challenges related to geographic dispersion. At the same time, increasing use of electronic systems and records and improvements in statistical assessments, present opportunities for alternative monitoring approaches (e.g., centralized monitoring) that can improve the quality and efficiency of sponsor oversight of clinical investigations.

FDA encourages sponsors to develop monitoring plans that manage important risks to human subjects and data quality and address the challenges of oversight in part by taking advantage of the innovations in modern clinical trials. A risk-based approach to monitoring does not suggest any less vigilance in oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing or mitigating important and likely risks to data quality and to processes critical to human subject protection and trial integrity.

Moreover, a risk-based approach is dynamic, more readily facilitating continual improvement in trial conduct and oversight. For example, monitoring findings should be evaluated to determine
whether additional actions (training of clinical investigator and site staff, clarification of protocol requirements) are necessary to ensure human subject protection and data quality across sites.

Source: FDA.

An FDA rule specific to medical devices proposed last year, but not yet finalized, would require companies to ensure their clinical trials meet U.S. standards, even if they were conducted in a nation with fewer rules on how clinical trials are conducted. U.S. regulators have also increased their scrutiny of payments made by companies and clinical research organizations to investigators looking for red flags of corruption, Foreign Corrupt Practices Act violations, and compromised results.

On the False Claims Act front, the Affordable Care Act's demand for crackdowns on Medicare and Medicaid fraud have swept some trials into its enforcement net. In one case, in August 2013, the Justice Department ordered Emory University to pay $1.5 million to settle claims that it violated the Act by billing Medicare and Medicaid for clinical trial services that were not permitted under the new rules.

Clinical Trial Audits

Regulators could also add new regulations on how audits of clinical trials are conducted. “Most clinical trials are audited by the individuals who are also doing the trial,” Weinberg says. “In a post Sarbanes-Oxley, post-Enron world, that makes no sense to me. There are two things people care most about: their health and their money. We changed all the rules so the guy who audits public companies can't also be the one who does the books, but we never changed the rules so that the guy who conducts a clinical trial cannot audit himself. It hasn't changed yet.”

Despite the regulatory changes afoot, Weinberg doesn't think companies should be too worried.

“There are countries that are becoming more stringent, creating their own standards and demanding adherence, but if you are in this business, you are in the game of regulation,” he says. “You can't afford to be lax in your standards anyway, because it has to eventually pass muster with the FDA. Every piece of data you collect has to go through the FDA anyway, and if that trial has been less than diligent, the next thing you know the agency is disapproving the drug and you have wasted millions of dollars.”