McDermott Will & Emery

China to Streamline Clinical Trials

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Recently, the Chinese government issued guidelines for Phase 1 clinical drug trials in an effort to make them safer, better organized and less time-consuming. International companies should identify and address the vital differences between the new Chinese regulatory framework and oversight systems in other countries and regions where they may conduct clinical trials.

With increasing investment in research and development by foreign companies in China, assuring the reliability and efficiency of the drug and device development process is a critical priority. However, this investment comes at a time of increasing concern over the efficiency and integrity of the clinical trial process in China and of complaints that the clinical trial stage of biomedical innovation has become a bottleneck for the licensing of new drugs and devices in China.

The Chinese government has begun to respond to these complaints and concerns. On 2 December 2011, the State Food and Drug Administration (SFDA), the government agency that has jurisdiction over all clinical trials in China, issued the Guiding Principles for Administration on Phase I Clinical Trials on Drugs (for Trial Implementation) (Guiding Principles), which aims to streamline Phase I clinical trials in China. This is an important development for industry and research sites involved in any stage of the biomedical innovation process.

The Guiding Principles became effective on the day they were promulgated (*i.e.*, 2 December 2011). Some observers take a skeptical view of the Guiding Principles as just a compilation of existing Good Clinical Practice statements. Other observers however, are more optimistic that the Guidelines can have a positive impact on the life sciences sector. From their perspective, the Guiding Principles are a prelude to reform of the entire drug licensing system in China. Optimists are encouraged, for example, by ongoing efforts of the SFDA to draft two regulations: the *Standards on the Administration of Quality of Drug Registrations* and the *Standards on the Administration of Drug Reviews* to streamline further clinical trials and the agency's own review process. These rules establish an Expert Advisory Committee in respect of drugs registration administration. In addition, internal and external supervisory mechanisms will be established to supervise the drug review and approval process. In short, the SFDA's efforts to make clinical trials safer, better organized and less time-consuming seem to be headed in the right direction. It remains to be seen whether or not the SFDA will issue similar guiding principles for Phase II, III and/or IV clinical trials.

In drafting the Guiding Principles, the SFDA referred to the *Guidelines for Phase 1 Clinical Trials* of the Association of the British Pharmaceutical Industry, and the *Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products* and the *Guideline for Good Clinical Practice* of the European Medicines Agency. These reference materials, as well as a translation of the Guiding Principles, are available upon request from any of the contacts listed below.

Safety Considerations

The Guiding Principles are intended to protect more effectively the rights and safety of trial subjects and to enhance the research quality and management of Phase I clinical trials. To achieve these goals, the Guiding Principles clearly delineate the rights and duties of sponsors, research sites (known as "laboratories") and ethics committees.

The Guiding Principles require that a person not participate in a trial unless the individual signs a letter of informed consent, but the principles do not specify what information must be included in the letter. Generally speaking, however, this informed consent document must specify the objective of the Phase I clinical trial and describe the possible benefits and risks. The Guiding Principles also require that a laboratory must maintain regular communication with the trial subjects in order to uncover any adverse events in a timely manner. A sponsor shall give appropriate economic compensation to a trial subject for his or her participation. In the event that a study participant is harmed on account of his or her participation in a clinical trial, the sponsor must assume the costs of treatment and provide reasonable additional compensation.

Requirements for Better Organization

A sponsor may only select qualified laboratories (*i.e.*, clinical trial bases where clinical trials are conducted) to conduct Phase I clinical trials. A qualified laboratory must meet the various requirements the SFDA issues (*e.g.*, the Guiding Principles) and be accredited by the China National Accreditation Service for Conformity Assessment in accordance with the Accreditation Criteria for the Quality and Competence of Medical Laboratories. A laboratory shall have adequate physical facilities and equipment, as well as quality management systems.

The laboratory director and principal investigator, if different, shall have at least five years' experience handling clinical trials. The laboratory director is the person in charge of the administration of a laboratory, while a principal investigator means the person responsible for a specific clinical trial project.

The Guiding Principles emphasise risk prevention and management. An ethics committee must closely monitor trial risks, trial plans, the informed consent form and process, the qualification and experience of laboratories and associated researchers, trial subject recruitment and adverse events. (An ethics committee is the counterpart of IRB

(short for Independent Review Board) in the United States.) The sponsors, researcher and ethics committee shall work closely together to manage and control risks.

A sponsor must evaluate any possible risk prior to a clinical trial, and reach a consensus with each participating laboratory regarding risk management.

In turn, an ethics committee shall review risk-control measures and monitor their implementation. The committee shall also have the right to suspend or terminate a clinical trial.

The original data shall be first-hand information obtained from the trial. The Guiding Principles also require that the equipment and methods used to generate study data shall be inspected and verified. However, they do not specify which party is responsible for inspection and verification.

The sponsor, principal investigator and laboratory director must each co-sign a final report that will be submitted to the Center for Drug Evaluation of the SFDA. In addition, the head of a laboratory shall sign the analysis report on any biomedical samples, which shall be signed off by the laboratory as well.

Efficiency Considerations

The Guiding Principles require that sponsors and laboratories enter into a research agreement to specify the interests and rights of each party. Among other terms, the agreement must specify funding terms, the scope and process of clinical trials, and any permitted sub-contracting.

A sponsor may engage a Contract Research Organization (CRO) to carry out some work and tasks, but the sponsor remains responsible for the sub-contracted work and tasks.

Below is a table highlighting each chapter of the Guiding Principles.

Chapter	Title	Highlights
1	General Provisions	The purpose of the Guiding Principles is to protect the rights and safety of trial subjects and to enhance the research quality and management level of Phase I clinical trials.
2	Duties and Requirements	A sponsor may only select qualified laboratories to conduct Phase I clinical trials. A sponsor may entrust a Contract Research Organization to carry out some

		work and tasks, but the sponsor shall be responsible for the sub-contracted work and tasks.
3	Implementation Conditions	An ethics committee shall closely watch trial risks, trial plans, informed consent, the qualification and experience of researchers, trial subject recruitment and adverse events. A laboratory shall have adequate facilities, organization and quality management systems. The study director and principal investigator of a laboratory shall have at least five years' experience handling clinical trials.
4	Management System and the Standard Operating Procedure	The management system of a laboratory shall cover the management of contracts, personnel, files, study products, trial places, facilities, instruments and equipment. The standard operating procedure (SOP) shall cover experimental design, implementation process, management of study products, handling of adverse events, data management, final reports and quality controls.
5	Quality Assurance	A laboratory shall establish an independent and complete quality assurance system.
6	Risk Management	The sponsors, researcher and ethics committee shall work closely together to manage and control risks. A sponsor shall evaluate possible risks prior to a clinical trial, and reach a consensus with the concerned researcher regarding risk management. A researcher shall communicate with the sponsor on risk-management measures. An ethics committee shall review the risk-control measures and monitor their implementation, and shall have the right to suspend or terminate a clinical trial.
7	Contracts and Agreements	A sponsor and a researcher shall enter into a commission contract to specify the interests and rights of each party to the contract in terms of funding, the scope and process of clinical trials, sub-contracting and so on.

8	Trial Plans	A sponsor and researcher shall reach an agreement on a trial plan, which is subject to the approval of the ethics committee. A trial subject shall be sufficiently informed of a clinical trial. A trial shall not be conducted unless the trial subject signs a letter of informed consent.
9	Management on Trial Subjects	A researcher must maintain regular communication with the concerned trial subjects in order to find any adverse events in a timely manner. A sponsor shall give appropriate economic compensation to a trial subject. In case of any harm incurred to a trial subject, the sponsor shall assume the costs of treatment and bear a reasonable additional compensation.
10	Administration on Study Products	Study product cannot be used for purposes beyond a clinical trial.
11	Administration and Analysis of Biological Samples of Clinical Trials	Biological samples for a clinical trial shall be collected, processed and preserved according to the clinical trial plan and the SOP. A plan shall be made on the analysis of biological samples—the plan shall not be put into performance unless the laboratory leader, study director and sponsor sign off on it.
12	Data Management and Statistics Analysis	The original data shall be the first-hand information obtained from a clinical trial. The equipment and the methods used to get those data shall be inspected and verified.
13	Final Reports	A sponsor and principal investigator shall co-sign a final report, which shall be also signed by the sponsor and the laboratory. The head of a laboratory shall sign the analysis report on biological samples, which shall be signed by the laboratory, as well.
14	Miscellaneous	The SFDA is responsible for interpreting the Guiding Principles. The Guiding Principles took effect 2 December 2011.

Next Steps

In light of the Guiding Principles, sponsors, laboratories and ethics committees may wish to consider taking the following courses of action:

1. International companies should identify important differences between the Chinese regulatory framework for clinical trials and oversight systems in other areas where they may conduct clinical trials, for example, the United States, European Union or India.

2. Sponsors and research sites should review their policies and procedures to ensure compliance with these new standards.

3. Sponsors and research sites should review their existing agreements and implement standardised agreements, tools and templates to facilitate compliance.

4. Sponsors and research sites should review their procedures for informed consent, as well as ensure the consents for active trials meet the new standards.

5. Sponsors and research sites should review the qualifications of their existing laboratories and CROs to ensure they meet the appropriate qualification standards. Robust due diligence procedures should be implemented for all new arrangements.

6. Ethics committees, sponsors and research sites should provide broad-based training regarding these standards and international best practices to accelerate innovation in China.

7. Sponsors and research sites should assess their risk mitigation plans for the conduct of drug and device development in China.

8. Sponsors and research sites should consider undergoing “mock” audits by third parties to identify gaps and weaknesses in their research programs requiring prompt attention.

9. Sponsors and research sites should consider how to leverage the Guiding Principles to speed up the process of a Phase I clinical trial.