China Issues Draft Guidance on Multi-Regional Clinical Trials

On November 21, 2014, China Food and Drug Administration ("CFDA") released a *Draft Guidance on Multi-Regional Clinical Trials (Provisional)* ("Guidance") for public comments through December 21. The Guidance aims to set forth clear requirements for multi-regional clinical trials ("MRCT") involving study sites in China. In the past few years, MRCT has emerged as a popular strategy for global concurrent drug development by multinational pharmaceutical companies, but its governance has not been fully addressed in the existing *Drug Registration Rules* ("DRR") and the *Good Clinical Practices for Drugs* ("GCP").

- General requirements

  The Guidance encourages sponsors to use MRCT to develop drugs for unmet medical needs and for serious life-threatening diseases in China. Furthermore, the Guidance recommends that MRCT sponsors consider conducting additional pivotal studies in China, or carrying out dedicated regional studies on Chinese patient groups.

  To initiate an MRCT with the CFDA, the sponsor must submit for its review the dossiers submitted to regulatory authorities in developed countries, including the complete study protocol and the supporting data. A uniform protocol must be observed to rule out inconsistencies of evaluation methods among cross-regional sites and investigators.

- Conditions for accepting MRCT data for drug registrations in China

  According to the Guidance, sponsors using MRCT data to support drug registrations in China must comply with the relevant sections in the DRR governing clinical trials. The Guidance also imposes additional requirements: First, the sponsor must conduct a holistic evaluation of the entire MRCT dataset and a trending analysis of the data from subjects in Asia and China. Specifically, the sponsor is expected to evaluate whether the enrolled Chinese subjects are representative of the relevant patient population in China. Second, the sponsor must ascertain whether the Chinese subject sample size sufficiently supports the conclusion that the study drug is safe and effective for Chinese patients. Third, the sponsor must adhere to internationally accepted GCP principles and ethical standards. They must also allow the CFDA to inspect the study sites from time to time, which can be any of the onshore or offshore sites involved in the MRCT.

  The Guidance explains further that, once the MRCT is concluded, the sponsor must submit to the CFDA the global study report, the statistical analysis report, the databases, and relevant supporting data, as well as the comparative and trending analysis of the data from Asian and Chinese subgroups against other subgroups.

- Other regulatory and technical requirements for sponsors

  MRCT sponsors must comply with the applicable regulatory standards of all countries or regions involved, such as rules concerning clinical trial authorizations by drug authorities, public registry and disclosure of trials, ethical reviews, informed consent, retention and transportation of biospecimens, collecting and evaluating adverse events, centralized data processing, CRO management, labeling and handling of investigational drugs, and administration of electronic data collection systems.

  The design of an MRCT's study protocol must also take into account all types of inter-regional differences, such as epidemiological factors, differences in medical practices, pharmacokinetics differences, choices of dosage and control drugs, evaluation criteria for therapeutic effectiveness, and sample size.

- Changes to study protocols

  The Guidance sets forth two types of changes to the study protocol of an MRCT after the approval by the CFDA: those that heighten the risk exposure for subjects and those that do not. The former involves, for example, adding dosage or prolonging the term for study, and requires a supplementary application with the CFDA for approval. The latter does not require a supplementary approval and only needs to be filed with the CFDA on record subsequent to the ethics committee approval. Adding or changing indications amounts to a new study and requires application with a new protocol.

The Guidance creates new substantive requirements regarding the conduct of MRCT, especially with respect to the use of MRCT data for drug registrations in China. Procedurewise, the Guidance does not clarify the ambiguity in the DRR as to how an MRCT should proceed to a new drug application or biologics application ("NDA" or "BLA"), the final drug marketing authorization in China. Specifically, the Guidance is silent on whether a separate IND application is still required if the MRCT data meets all the substantive requirements to be accepted for the NDA or BLA review in China. Pharmaceutical companies are advised to review the draft Guidance and propose their comments or questions to the CFDA for better clarification about the procedural requirements.

If you would like to discuss the foregoing or any other related matter, please contact Katherine Wang, Mark Barnes or your usual Ropes & Gray advisor.