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CLINICAL TRIALS HANDBOOK Asia Pacific



CHINA

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China

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Introduction

The China Food and Drug Administration (CFDA) used to be the central regulatory body in China for pharmaceuticals, medical devices, health food and cosmetics. After the State Council's major institutional reform in early 2018, many departments have now become under the new super-regulator, the State Administration for Market Regulation (SAMR). Among the multiple responsibilities of SAMR is the supervision of the newly formed China National Drug Administration (CNDA), which continues to be responsible for the administration and regulatory enforcement of pharmaceuticals, medical devices and cosmetics. Even as the CFDA has been dismantled in early March, we will still refer to the pharmaceutical regulator as the CFDA for purposes of this summary.

Certain tasks, such as preliminary processing for certification and registration applications, and supervision and enforcement at the local and provincial levels, are delegated by the CFDA to the provincial level Food and Drug Administration (FDA). However, the CFDA (located in Beijing) remains the central governing body for all regulatory authorities for pharmaceuticals, including clinical trials/study for new/imported drugs and devices.

Regulatory framework

The main laws and regulations governing clinical trials of pharmaceuticals are as follows:

- The Law for Administration of Pharmaceuticals ("**Pharmaceutical Law**") (2015) and its Implementation Regulations ("**Implementation Regulations**") (2016)
 - The Pharmaceutical Law and its Implementation Regulations provide the basic legal framework on manufacturing, distribution, packaging, pricing, advertising, inspection and other regulatory matters on pharmaceuticals.
- Measures for the Administration of Registration of Pharmaceuticals ("**Registration Measures**") (2007)
 - The Registration Measures provides detailed rules governing process of drug registration, including clinical trials onsite inspection and registration approval.
- The Administrative Regulations of Pharmaceutical Clinical Trials ("**China GCP**") (2003)
 - The regulation is China's implementation of the ICH Guideline for Good Clinical Practice (ICH GCP) (promulgated by the CFDA).
 - The CFDA put forward in 2016 a draft amendment to the 2003 GCP for public consultation.
- Measures for Certification of Qualification of Clinical Trial Centers for Pharmaceuticals ("**Center Certification Measures**") (trial version) (2005)
 - Center Certification Measures provides detailed rules governing qualification requirements and certification procedure for clinical trial centers.
 - The CFDA put forward in 2015 a draft Center Certification Measures for public consultation.
- Guiding Principles for Ethical Review on Pharmaceutical Clinical Trials ("**Ethical Review Principles**") (2010)

- The Ethical Review Principles provide detailed rules governing the organization, management and responsibilities of ethics committees (**ECs**) and the procedures and standards applied by ECs in the ethical review.
- Guidance on International Multi-Centre Clinical Trials ("**MCCT Guidance**") (trial version) (2015)
 - The MCCT Guidance provides general principles on the bases, strategies, country-specific requirements, scientific considerations, ethics, protocol amendment, product registration, and onsite inspection in relation to international multi-center clinical trials.
- Guiding Principles for General Considerations in Pharmaceutical Clinical Trials ("**Clinical Trial General Considerations**") (2017)
 - The Clinical Trial General Considerations refer to the ICH version and describe considerations on the principles and methodologies for overall and specific strategies on clinical trials.
- Guiding Technical Principles for the Acceptance of Overseas Clinical Trial Data of Pharmaceuticals (2018)
 - The Guiding Technical Principles set out the general criteria and considerations in the acceptance of clinical trial data generated overseas.
- Adjustment on the Review and Approval Procedures for Clinical Trials for Pharmaceuticals (2018)
 - This Adjustment on the Review and Approval Procedures for Clinical Trials adopts a negative notification system for clinical trial approval (**CTA**), in place of the previous positive approval system. It also establishes a communication mechanism between applicants and technical experts of the Centre for Drug Evaluation (**CDE**), which is a group within the CFDA in charge of technical review, before and throughout the clinical trial review and approval process.

The rules governing clinical trials involving molecule-based Investigative Medical Products (IMPs) or new chemical entity and biologically based IMPs are essentially the same but require more stringent drug evaluation that involves assessment by an FDA-approved evaluation center.

General considerations

Important considerations for clinical trials, as provided by the CFDA, include the following:

- Protection of subjects and safety considerations – Full assessment on risks to humans should be made before the trials, on the basis of product R&D data and pre-clinical trial data. The number of subjects and the observation period should be determined based on the probability of adverse events and the time of occurrence of adverse events.
- Bases for clinical trials – Comprehensive assessment on non-clinical and pre-clinical toxicological and PK/PD data should be made in relation to factors such as the proposed doses and exposure period, properties of drugs, target indication, target population and route of administration.
- Purpose-oriented trials – The protocols should be designed based on the purpose of each phase of the trials (i.e., PK/PD assessment trials, exploratory trials, verifying trials or post-marketing trials).
- Considerations of individual trials – For an individual trial, considerations should be given to the number of subjects, the selection of subjects, the selection of comparison drugs or placebos, methodologies, criteria, and indicators of study.

- Analysis of result – Scientific statistical method should be adopted and be in strict accordance with the protocol. Detailed reasons for the exclusion of any subjects should be specified.

Clinical trial agreements

The permissions/notifications that are required to conduct a trial are as follows:

1. CTA issued by the CFDA
2. Approval from a competent EC or Institutional Review Board (IRB)

A sponsor is responsible for obtaining the CTA. For foreign sponsors, they usually act through local CROs to obtain such approval. The investigator is responsible for obtaining EC or IRB approval, as well as informed consent of the subjects.

The investigator is responsible for informing relevant authorities (the local FDA and the National Health & Family Planning Commission) of any serious adverse events (SAEs). In practice, the clinical trial agreements will inevitably require the investigator to report any SAE to the sponsor.

Under Chinese law, insurance taken out by the sponsor to cover any injuries to the test subject due to the study drug is mandatory. However, there is no requirement to take out local insurance for that purpose. Usually, global clinical trial insurance that includes China will be sufficient.

A sponsor shall provide insurance for the test subjects participating in the clinical trial and cover the expenses of treatment and corresponding compensation for the subjects who sustain injuries due to the study drug.

The China GCP basically implements the requirements under ICH GCP Guideline 2003, but there are some specific requirements in the China GCP that are not in the ICH GCP Guideline, such as the following:

Sample size minimum requirement:

- Chemical drugs – Phase I: 20-30; Phase II: 100; Phase III: 300; Phase IV: 2000
- Biological drugs (therapeutic) – Phase I: 20; Phase II: 100; Phase III: 300; Phase IV: no requirement
- Biological drugs (preventive) – Phase I: 20; Phase II: 300; Phase III: 500; Phase IV: no requirement

The sponsor will be required to indemnify the investigator for his loss as a result of the latter's participation in the clinical trial, except for medical malpractice. In practice, it is common to have such indemnity clause in a clinical trial agreement.

There are no specific legal or regulatory requirements governing publication of the study results, and parties are free to agree on how they would like to publish the study results.

It is common practice for the sponsor to require investigators to refrain from publishing the results even of relevant studies without the express consent from the sponsor. This is especially important to ensure that there is no public disclosure of a patentable invention before a patent application is filed.

Clinical trial agreements are not subject to review by regulatory authorities but in some cases, the EC or IRB may review the clinical trial agreements.

Clinical trial approval

Under the CFDA's Adjustment on the Review and Approval Procedures for Clinical Trials for Pharmaceuticals issued in July 2018, the CFDA now adopts a negative notification system for the CTA in place of the previous positive approval system, shortening the time for the CTA from the previous 6-18 months to 60 business days. Furthermore, a communication mechanism was established between applicants and the Centre for Drug Evaluation (the department within CFDA that reviews and approves drug applications and grants CTAs) before and throughout the application. The process can be summarized as follows:

- An applicant should file a meeting request with the CDE regarding the feasibility of a trial, submitting materials including a draft trial protocol and all pre-clinical data.
- The CDE experts will review the materials and raise comments and questions.
- The applicant may cancel the meeting request if it believes all issues raised in the CDE comments have been resolved, or it can continue with the meeting request if there is a need for discussion.
- The applicant may discuss key technical issues with the CDE experts in a meeting and decide if it is ready to conduct the trial.
- The applicant may then file an application for the CTA.
- The CDE will make a formality review within five days and issue a notice of acceptance.
- The applicant can proceed to do the trial directly if it does not receive negative comments from the CDE within 60 business days.
- The CDE will raise negative comments if it finds that the materials fail to meet technical requirements, and the applicant will be given a chance to supplement materials to address the issues raised; the applicant can proceed with the trial directly if it does not receive negative comments within 60 business days thereafter.
- If the applicant fails to supplement materials to meet the technical requirements, the CDE will issue a notice to suspend the trial.
- The applicant can apply to continue the review and approval process after it has resolved the issues raised by the CDE.

Ethical review by an EC

Under the Ethical Review Principles, an EC should be a gender-balanced panel composed of at least five persons of different backgrounds, including pharmaceutical professionals, non-pharmaceutical professionals, legal experts and independent members.

An EC has the authority to carry out the following:

1. Approve or disapprove a clinical trial
2. Track and review the status of a clinical trial
3. Terminate or suspend an approved clinical trial

The following documents are required for an EC approval application:

- An application form
- The clinical trial protocol
- Informed consent forms
- Materials in relation to the recruitment of subjects
- Case report forms
- The investigator's brochure
- Résumés of the main investigators
- Approval for Clinical Trial issued by the CFDA
- Explanation on previous important EC decisions for the trial in question
- Qualification test report of the investigational products

The ethical review involves the following aspects:

- The design and implementation of protocols
- Risks and benefits of the trial
- Recruitment of subjects
- Information communicated by the informed consent forms
- The process of obtaining informed consent
- Diagnosis and protection on subjects
- Privacy and confidentiality
- Study involving vulnerable groups

The EC should hold full discussions before making any decisions regarding approval, disapproval, suggestion of amendment, termination or suspension in relation to a proposal, a proposed amendment to a protocol, or the clinical trial.

The EC is also responsible for monitoring and tracking the progress of the trial. During the annual or periodical review, the EC should: check on the number of subjects recruited, completed or excluded from the trial; watch any event or new information that may have impact on the risks and benefits of the trial; and make a report if serious adverse events are identified.

In addition, the EC should also review and make decisions regarding violation or non-compliance of the protocol, early termination of the trial, and the final conclusion of the trial.

Sponsor and contract research organizations (CROs)

The legal functions of a sponsor include the following:

- Initiating, applying, organizing, monitoring and auditing a clinical trial and providing the trial funds
- Selecting a certified institution and investigators for the trial
- Designing the protocol, together with the investigator; providing brochures regarding investigative drugs
- Providing qualified study drugs, standard products, comparison pharmaceuticals or placebos
- Appointing qualified personnel to monitor the trial
- Establishing quality control standards and a quality assurance system for the trial
- Investigating, reporting and adopting remedial measures promptly (together with the investigators) on serious adverse events that happen in relation to the trial
- Submitting the final trial report to the CFDA
- Notifying the investigators, the EC and the CFDA and stating the reasons therefor before suspending a clinical trial
- Providing insurance for the trial subjects, and undertaking the expenses of treatment and the corresponding economic compensation for the subjects who are injured or have died as a result of the trial; providing legal and economic indemnity for the investigators, except in circumstances caused by medical malpractice
- Pointing out any deviation or violation of the investigators and requesting correction or ceasing of the clinical trial, and reporting the matter to the competent FDA in case of serious violations

A sponsor need not be located in the country where the clinical trial is conducted.

A foreign sponsor is required to retain a local agent that can either be its local representative office (e.g., a subsidiary company or branch office) with a valid Chinese business license or a local CRO (authorized by a Power of Attorney) when applying for and conducting a trial.

The sponsor may entrust to a CRO the conduct of the trial. However, for foreign sponsors, they must retain a local agent, usually a CRO, to apply for and conduct the trial. Normally, the CRO in China can provide full services, such as selecting investigators, filing applications for trial approval, designing study protocol, preparation of investigator brochures, monitoring the progress of a trial, processing and analyzing trial data, and preparing the final report.

However, the ultimate legal responsibility still rests with the sponsor, even if most of the work is done by a CRO.

There are no specific laws or regulations relating to the selection and/or appointment of a CRO.

Investigators

An investigator is responsible for the following:

- Obtaining and maintaining necessary certification for conducting the trial
- Conducting the trial in strict accordance with the trial protocol

- Explaining the benefits and risks of a trial and obtaining voluntary informed consent forms from trial subjects
- Making medical decisions on the clinical trial and ensuring that the trial subject will receive proper treatment in case of any adverse events during the trial period
- Taking necessary measures to ensure the safety of the trial subject and in the event of any serious adverse events, adopting appropriate treatment measures and reporting the SAE to the local FDA and the local National Health & Family Planning Commission office within 24 hours, as well as to the EC/IRB as soon as practicable
- Properly filling out a case report form and keeping a record of trial data in an accurate and timely manner
- Cooperating with the auditor appointed by the sponsor or the CFDA for the auditing and inspection to ensure the quality of the clinical trial
- Not charging the trial subject for investigational products
- Completing a trial report and sending the same to the sponsor after the clinical trial

Study drugs

- Most blood products and biological products should be evaluated by a drug evaluation institute approved by the CFDA; for chemical drugs, there is no such requirement. The CFDA will accept relevant safety information (e.g., data on toxicology, stability) contained in the investigational drug brochure issued by the sponsor.
- In the course of a clinical trial, study drugs shall only be used on the subject of the clinical trial and be provided to the trial subject free of charge.
- The dosage and the usage method shall conform to the protocol. Unused study drugs shall be returned to the sponsor. The investigators shall not turn over the investigational products to any person not authorized to participate in the clinical trial.
- A sponsor shall be responsible for packing and labeling properly the study drug and indicating clearly that they are for clinical trial only. In double-blind clinical trials, the study drugs shall have the same packing and labeling as the comparison drugs or placebos.
- The usage record of the study drugs shall include certain information on the quantity, shipping, delivery, acceptance, distribution, as well as on callback and destruction of any unused drug after the investigation.
- The provision, usage, storage and disposal process of investigational products, as well as the disposal process of residual products shall be subject to examination by relevant personnel.
- The study drug shall be used only for the purpose for which it is intended. Any unused study drugs shall be returned to the sponsor. Therefore, upon completion of the clinical trial, the investigator shall immediately return all unused study drugs to the sponsor and shall not provide the same to the trial subjects.

Intellectual property (IP) and data

There are no explicit legal or regulatory guidelines governing ownership of inventions and other IP rights resulting from the trial.

It is common practice for the IP clause in a clinical trial agreement to include the following:

- Ownership of all IP belonging to the sponsor, but for whatever reason cannot be owned by the sponsor, the investigator/institution shall license to the sponsor
- No additional compensation payable to the investigator for the assignment or license of IP
- A “notify and assist” clause stating that the investigator/institution shall notify the sponsor of any new invention and assist in perfecting the formalities in assigning or licensing of such invention

Investigator-initiated trials are allowed. It is more common to have investigator-initiated trials in local marketing studies where in many cases, CFDA does not need to be informed. If, however, the trial is an investigative trial relating to the efficacy or safety of a drug, then CTA is required.



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