**Key Points and Determination Principles for**

**Drug Registration Inspection**

**(Drug Clinical Trials)
(Trial)**

In order to ensure the quality of drug registration inspection and unify the inspection scope and determination criteria, in accordance with the *Drug Administration Law* *of the People’s Republic of China*, the *Provisions for Drug Registration, Good Clinical Practice* and other laws and regulations as well as relevant guidelines, the Key Points and Determination Principles for Drug Registration Inspection (Drug Clinical Trials) (Trial) is hereby formulated.

**I. Purpose**

On-site inspection for drug registration (Drug Clinical Trials) is mainly aimed at evaluating whether the clinical trial execution, data recording and result reporting conform to the trial protocol and relevant regulations of drug clinical trial, verifying the authenticity and consistency of relevant application dossiers, and paying attention to subject protection, by checking and/or on-site inspection of the original data and documents of the application dossier and clinical trials.

**II. Scope**

(I) It is applicable to the on-site inspection of drug clinical trials under the on-site inspection of drug registration development initiated by the Center for Drug Evaluation, NMPA and organized and implemented by Center for Food and Drug Inspection of NMPA. Which institutions to be inspected shall be determined based on registration requirements and risk principles. On-site inspection of phase IV and other drug clinical trials initiated by CDE shall be implemented by referring to the inspection points.

(II) On-site inspection of drug clinical trials refers to the on-site check and verification of the clinical trials in the registration application dossiers. It mainly verifies the investigators’ performance of duties, including subject protection, the implementation of trial protocols, data records and result reports. Based on registration requirements and risk principles, the inspection may only conduct on part of the inspection points. If necessary, the sponsor, the contract research organization or the preparation conditions of investigational drug may be subject to on-site inspection, and the investigational drug may be subject to sampling inspection.

**III. Key Points for On-site Inspection of Clinical Trials**

(I) Clinical trial license and conditions

1. To conduct clinical trials, the approval from the drug administration shall be obtained, and the bioequivalence test shall be filed as required.

2. Have the approval letter of the Drug Clinical Trial Ethics Committee.

3. Drug clinical trials are carried out in drug clinical trial institutions with corresponding conditions and filed as required (hereinafter referred to as the “clinical trial institution”). Among them, vaccine clinical trials are implemented or organized by tertiary medical institutions or disease prevention and control institutions at or above the provincial level that meet the conditions prescribed by the NMPA and the National Health Commission.

4. The site where the clinical trial is actually conducted is consist with that in the application dossier, having facilities and equipment required for clinical trials, and with verification, calibration and routine maintenance meeting the requirements and effectively operating medical emergency facilities.

5. The clinical trial institution and professional institutions formulate management documents adapting with the work, and perform in accordance with the documents. The management documents shall meet the requirements of the relevant regulations and guidelines, and cover the whole process of the clinical trial.

6. The participants in all aspects of clinical trials shall be qualified in education, training and experience correspondingly to undertake the work of clinical trials, and shall be authorized by the principal investigator.

7. The investigator, clinical trial institution and sponsor shall sign a clinical trial contract before the start of the trial to agree on the relevant rights and obligations.

8. The sponsor/contract research organization (CRO) has performed its corresponding responsibilities in accordance with the Good Clinical Practice (GCP), the clinical trial protocol and the contract, and stores the relevant documents and records.

9. Clinical laboratories of medical institutions shall ensure the integrity and effectiveness of the detection system, and regularly calibrate the inspection instruments that needs to be calibrated, the auxiliary equipment that has an impact on the clinical inspection results and other equipment required in clinical trials.

10. The clinical laboratory of a medical institution shall participate in the inter-laboratory quality evaluation of clinical laboratory organized by the inter-laboratory quality evaluation institution recognized by the national health department and obtain the certificate of “PASS”.

(II) Ethical review

1. The number and background of attendees of the Ethics Committee for project review meet the regulatory and SOP requirements.

2. The ethical review is conducted according to relevant regulations and SOP rules, with written records retained, and the meeting time and discussion content shall be indicated, voting votes of members of the Ethics Committee and the review conclusions shall be kept intact and consistent with the approval letter of the ethical review.

3. The Ethics Committee pays close attention to whether injuries of subjects receive timely medical treatment, and monitors whether the sponsor and the investigator timely delivers the compensation to the subjects.

4. The design of trial protocol meets the requirements of GCP in China, and the design of the diary cards and questionnaires related to the trial shall meet the requirements for clinical trial data collection and traceability.

(III) Implementation process of clinical trial

1. Signing of informed consent form

(1) The contents of the informed consent form comply with the requirements of GCP.

(2) All of the screened subjects sign the informed consent form.

(3) The signatures of the subject and/or the guardian (if necessary), the investigator, and impartial witness (if necessary) and the time of signature in the informed consent form and the version of the informed consent form meet the requirements of GCP.

(4) The signing time of informed consent form shall not be earlier than the ethical approval time, and the screening time shall not be earlier than the signing time of informed consent form.

(5) The investigator or designated researcher who explains the contents of the trial to the subject or his guardian and obtains informed consent should be an authorized researcher and have the qualification to practice in this hospital.

2. Subject Screening, Enrollment and Protocol Implementation

(1) There shall be source data to confirm that all the subjects actually participate in the clinical trial.

(2) Subject screening complies with the inclusion/exclusion criteria specified in clinical trial protocol and retain sufficient supporting evidence for the subjects enrolled.

(3) The investigator follows the randomization procedure specified in the clinical trial protocol.

(4) Blind trials (if any) are set up, kept blind and unblinded according to the requirements of the trial protocol; accidental unblinding or emergency unblinding due to SAE (serious adverse events) should be unblinded according to the emergency unblinding procedure and explained in writing by the investigator.

(5) The investigator implements the trial (such as visit, drug administration, blood drawing, safety examination and efficacy evaluation, etc.) in accordance with the trial procedures and evaluation methods specified in the clinical trial protocol, takes measures to ensure accuracy of the execution of key steps, and keeps the relevant records, for example, deviation from the trial protocol shall be recorded and explained, and records of concomitant medication or concomitant therapy and prohibited drugs comply with the requirements of the protocol.

3. Handling and reporting of safety information

(1) The relevant medical judgement and clinical decision making are executed and recorded by qualified medical professionals in this institution.

(2) The investigator shall keep intact records of AE (Adverse Event), SAE and judgement criteria of drug correlation, meeting the provisions of trial protocol and medical routines.

(3) The investigator shall ensure that the subjects with AE and SAE receive timely and reasonable treatment.

(4) Except for SAEs that do not require immediate reporting as specified in the trial protocol or other documents, the investigator shall immediately report all SAEs to the sponsor in writing, and then provide a detailed and written follow-up report in a timely manner.

(5) For the report involving death events, the investigator shall provide the sponsor and the Ethics Committee with other required materials, such as autopsy report or final medical report.

(6) For reporting of unexpected serious adverse reaction (SUSAR) during the drug clinical trial and safety updates during the development, the sponsor shall report to the drug evaluation agency, the Ethics Committee and other institutes in accordance with the requirements of relevant procedures and regulations specified in Standards and Procedures for Quick Reporting of Safety Data During Drug Clinical Trials.

4. Clinical trial data recording and reporting

(1) The management of source files related to clinical trials shall meet the medical requirements, and the source data shall meet the common criteria for the quality of clinical trial data (ALCOA+).

(2) Where the electronic medical record has already been adopted in daily diagnosis and treatment, the clinical trials shall use electronic medical records.

(3) For clinical trials with patients as subjects, relevant medical records shall be recorded in the outpatient or inpatient medical record system. The specific time and person who gives informed consent shall be recorded in the medical history record.

(4) Modifications to the data in the source data and CRF shall be traced, not obscure the initial data, retain the tracks of modification, explain the reasons, and sign and date by the modifier.

(5) Filling in and modification of the case report forms shall be in accordance with the guidelines provided by the sponsor, the data in case report forms and other reports are accurate, complete, clear and timely, consistent with that in the source files.

1. The relevant data of AEs recorded in the case report form and summary report (or database) are consist with the source data, without omission, misjudgment and error in recording.
2. The relevant data of SAEs recorded in the case report form and summary report (or database) are consist with the source data, without omission, misjudgment and error in recording.

(8) The number of cases screened, enrolled and completed clinical trials in the summary report of application dossiers shall be consistent with the number of cases in the actual clinical trials.

(9) Subject screening failure, dropout, discontinuation, withdrawal and exclusion shall be executed in accordance with the requirements of clinical trial protocol, record the actual circumstances and keep the original records, with intact chain of evidence, and consistent with those in the summary report.

(10) Data consistency between source data, CRF, database and application dossier.

5. Traceability of clinical trial data

(1) The enrollment, informed consent, medical history or concomitant disease, visit, drug administration, disease record and other information in the case report form are consist with the source data and/or and HIS system.

(2) The concomitant medication and concomitant treatment recorded in the summary report are traceable in HIS system, medical records or subject diary cards.

(3) The medical examination data from clinical laboratory, imaging department, ECG room, endoscopy room of the clinical trial institution in the case report form are traceable in LIS, PACS and other information systems or instruments and equipment of the institution.

(4) The efficacy and safety data obtained through the investigator’s evaluation are traceable to the evaluator, evaluation time, the original evaluation results and their modification.

(5) Where the results of subjects’ self-evaluation are regarded as the efficacy and safety data results, it can be traceable to the original evaluation records signed by the subjects (such as subject diary card, subject self-evaluation report and etc.)

(6) The subject number, drug administration cycle, administration order, types of preparation and other information are consistent with the source data.

(IV) Management of investigational medicinal products

1. There are proof of origin, certificate of analysis, and documentation of manufacture under GMP conditions of investigational medicinal products.

2. Investigators and clinical trial institutions designate qualified pharmacists or other personnel to manage investigational medicinal products.

3. There are records retained for the receipt, storage, distribution, use, recovery, return and unused disposal of investigational medicinal products (such as authorized destruction).

4. The conditions during the transportation and storage of investigational medicinal products meet the requirements of the protocol.

5. The quantity of investigational medicinal products used, the remaining quantity and other circumstances (such as loss and authorized destruction) is consistent with the quantity provided by the sponsor.

6. The batch number of investigational medicinal products in various records of drug management is consistent with the drug inspection report, summary report and other data.

7. The investigator randomly samples the investigational medicinal products of the bioequivalence test, and retains the sample as specified.

8. Abnormal circumstances occurred in various aspects of the management of the investigational medicinal products are timely evaluated, handled and recorded.

(V) Management of biological sample

1. Management of various aspects such as collection, handling, storage and transportation of biological samples complies with corresponding regulations, with records retained.

2. The conditions of collection, handling, storage and transportation of biological samples comply with the requirements of the clinical trial protocol.

3. The identification of the sample container is easy to distinguish and is unique, and does not disclose the privacy of the subject and type of preparation.

4. Abnormal circumstances occurred in various aspects of the management of the biological samples are timely evaluated, handled and recorded.

(VI) Central laboratory and independent evaluation agencies

1. For relevant inspection items used for medical judgement and used as efficacy and safety index, the reliability of the test results is verified by national inter-laboratory quality assessment or other methods.

2. The central laboratory establishes the clinical test report issuing system (including critical value reporting system), and reports the test results to the investigator according to relevant requirements, ensure the accuracy, timely and intact of the test reports, and guarantees subject privacy.

3. A laboratory quality management system is established for the central laboratory.

4. There are complete records for the process of receipt, processing, inspection and testing, storage, return (if applicable) and destruction of samples to be tested.

5. The sample to be tested is tested in a timely manner according to the requirements of the protocol and SOP, and the re-test is conducted in accordance with the trial protocol and relevant SOP of the laboratory.

6. The test method has been verified/validated and meets the requirements of the protocol, and the methodological inspection/validation original test records have been preserved.

7. The records of use, maintenance and calibration of instruments and equipment are complete. The enterprise keeps the records of instrument validation, use of instruments and equipment, and inspection and maintenance.

8. Institutions (such as independent imaging evaluation center, endpoint event determination committee, endpoint case judgement committee, data and safety monitoring board) conducting independent evaluation for clinical trial data carry out the evaluation process, data recording and modification according to relevant guidelines and their charters, and SOP.

9. Personnel conducting independent evaluation for clinical trial data have the corresponding qualification and meet the requirements of the relevant guidelines or their charters of the evaluation agencies.

10. The independent evaluation results can be traceable to the evaluation reports issued by each evaluator.

(VII) Collection and management of clinical trial data

1. The paper records (notebook, recording paper) are under controlled management, and reforms are under version control. The modification of the record keeps the initial record clear and discernible, indicates name of the modifier, modification date and reason.

2. Electronic data collection system passes the system verification, and retains verification record. Set user management, role management and permission management for the computerized system, different personnel or roles have the unique logon rights. With audit track function, it can display the records of modification data and modification reason.

3. If data conversion occurs during data processing, ensuring that the converted data are consistent with the original data and the data conversion process is visible.

4. Data traceability is ensured for external data.

5. The conditions and process of database locking comply with the SOP for database locking.

6. There is clear documentation for the database locking process and time. For blinded clinical trials, unblinding can be performed only after the database is locked.

(VIII) Entrusted study

1. For all the research, testing and other work involving clinical trials conducted by other departments or units, there is entrustment agreement/contract, and the responsibilities and obligations of entrusting party and entrusted party are clarified. The entrusting party, time, project and protocol reflected in the entrustment agreement/contract are consistent with those recorded in the application dossier. The report or chromatogram and other study results issued by entrusted institution are original copies affixed with official seal. Conduct on-site inspection on entrusted institution according to review requirements to confirm its study conditions and study situation.

**IV. On-site inspection points of biological sample analysis**

(I) Analysis conditions and compliance of biological samples

1. The analysis and testing unit is qualified to perform the analysis items of biological samples.

(1) There is reasonable organization setup and an organization chart. The laboratory personnel have clear division of responsibilities, are qualified in and capable of undertaking their works, have received training on GCP and other professional training. The principal investigators have corresponding professional background and experience.

(2) Formulate the management system documents in accordance with the analysis, and perform correspondingly. The contents of the management system documents comply with the requirements of laws, regulations and guidelines, and can cover the main processes of laboratory management and analysis item.

(3) QA department can independently perform the quality assurance duty, and is staffed with appropriate personnel suitable for conducting its work. The QA personnel with relevant qualification, are responsible for auditing each item and retaining intact records such as audit contents, problem identified, measures taken, and follow-up reexamination.

(4) The laboratory is divided into different functional areas, has reasonable layout, designed to prevent cross contamination, and there is the location map.

(5) It is equipped with instruments and software for sampling, weighing, formulating, testing and data analysis, which are meeting the requirements of analysis and testing. The range, accuracy and resolution of instruments and measuring tools meet the requirements of corresponding technical indicators, the model and number of the instruments are recorded in the original records, consistent with those in the application dossier.

(6) The instruments and equipment are specifically managed by the designated person, and there are intact records of use, calibration, maintenance and repair for the main instruments. The instruments used for testing shall at least go through installation qualification (IQ), operation qualification (OQ) and performance qualification (PQ), and have relevant records retained. Periodic examination and calibration shall be carried out for instruments and equipment that have direct impact on the testing results, and the relevant records shall be retained.

(7) It is equipped with ambient temperature and humidity monitoring device, and retains the temperature and humidity records. The refrigerator needs to be equipped with temperature monitoring and alarm system, and retains the temperature records and handling records after the alarm. It has sound power supply system and emergency response plan after blackouts.

(8) It is equipped with corresponding safety protection, emergency and first aid facilities and equipment.

(9) It has facilities and handling measures for collecting chemical reagents and bio-waste.

2. The analysis and testing unit and the sponsor or contract research organization (CRO) sign the entrusted contract, which specifies the responsibilities, rights and interests of the trial parties, and the potential interest conflicts shall be avoided by various parties.

3. The sponsor and CRO undertake their responsibilities according to GCP principles, protocol and provisions of the contract, and retain the relevant documents and records.

(II) Execution of the analysis experiment of biological samples

1. Management of the reference materials

(1) The reference materials are specifically managed by the designated person, with reliable and traceable source, and are stored and used under the conditions specified by the Certificate of Analysis (CoA) or the equal supporting documents. Check the original records of transportation, receipt, storage, picking, weighing, use, return, and destruction, and the information and records are intact.

(2) The area or equipment (refrigerator, freezer, and etc.) for storing reference materials is under controlled management, and the actual storage conditions and locations are consistent with the original records.

(3) Status of the reference materials and information on the original packing label are consistent with the regulations specified in CoA or the equal supporting documents.

2. Management of test sample and blank matrix

(1) The test sample and blank matrix are specially managed by the designated person, the room for receiving test samples has enough space for sample receipt, inventory and registration. Check the original records of transportation, receipt, inventory, stocking, storage, picking, weighing, use, return, and destruction, and the information and records are intact, with clear time and signature of the operator.

(2) The test samples are collected, transported, stored and tested through verified methods.

(3) The area or equipment (refrigerator, freezer, and etc.) for storing test samples and blank matrix is under controlled management, and the actual storage locations are consistent with the original records.

(4) Store the test samples within the specified time limit, the information on the label of the test sample is complete, clear and discernable, consist with the provision of the clinical trial protocol. Check the conformance of the test samples in terms of retention quantity and receiving quantity, testing quantity, and transfer quantity of the test sample.

3. Implementation of method validation

(1) Method validation items are examined according to the provision of the validation plan, there are the test method, experimental process and result records in the original records, which are consist with those in the application dossier.

(2) There are original weighing records for the reference materials, and original records of formulating time and process for stock solution and working solution, mobile phases and dilution, which are consist with those in the application dossier.

(3) There are original records of formulation, sub-packaging, storage, picking, use, return and etc. for correction samples and quality control samples, and original records of formulating time, placement location, storage conditions, stability time, and etc. for stability quality control samples, which are consist with those in the application dossier.

(4) Records of the preprocessing steps and key time points of the biological samples are complete and consist with those in the application dossier.

(5) All samples introduced into the instruments are recorded in the original records, and investigation and analysis is conducted for abnormal circumstances occurred during the process of method validation, which are consist with those in the application dossier.

4. Implementation of the analysis and testing of the test sample

(1) The test sample analysis is conducted according to the analysis plan, the preprocessing and testing method of the samples in the analysis batch are consist with the method validation, and the plasma concentration data is consistent with that in the application dossier.

(2) All the samples in one analysis batch are processed and extracted in the same order with that of the introduction, and the process is traceable. In the case of batch processing, every processing batch shall contain quality control samples of low, medium and high concentration, and comply with the predefined acceptance criteria.

(3) Within one analysis batch, all samples have a unique identifier, and are introduced continuously in sequence, if there is interruption, the reason for interruption is recorded in the original records, consist with the application dossier.

(4) Samples introduced into all the instruments are recorded in the original records, and investigation and analysis are conducted for abnormal circumstances occurred during the process of sample analysis, consist with the application dossier.

(5) If there is residual during the process of test sample analysis, evaluate the impact on the concentration of the test sample and carry out specific measures, consist with the application dossier.

(6) For bioequivalence test, all samples of the same subject are tested in the same analysis batch (except in special circumstances).

(7) For bioequivalence test, the sample analysis and data transfer are kept blinded.

(8) The reason for reanalysis of test samples and their reporting value selection comply with the standard operation procedures or provision of the analysis plan. The records of initial value, reason for reanalysis, number of repetition, results of reanalysis, the value finally accepted and reason for acceptance of the test sample are consist with those in the application dossier.

(9) The samples selected for incurred sample reanalysis (ISR) are representative, and the quantity meets the relevant requirement. If ISR meets the acceptance criteria, however, there is significant or systematic difference between results of multiple samples (for example, all samples of the same subject fail, all samples of the same analysis batch fail), investigation shall be conducted to determine the cause.

5. Chromatogram integration

(1) Chromatogram adopts automatic integration; the same integration parameters are used in the same analysis batch. If reintegration and manual integration of chromatogram are adopted, record the reason of modification and retain the original and reintegrated chromatogram and data, which are consist with the application dossier.

(2) If reintegration is conducted for standard curve and the quality control chromatogram, verify whether the reintegration impacts the acceptance of the analysis batch.

(3) Extract part of the electronic chromatograms of the test sample, accompanying standard curves and QC samples as well as method validation sample, which are consist with the application dossier.

(III) Management of records

1. Records (paper and electronic) include but not limited to: receipt and process records of the sample, preparation and analysis records of the sample, original chromatogram, deviation report, investigation report, standard operation procedures, audit track, and correspondence with the sponsor or the clinical trial institution, and the information recorded is authentic, accurate, intact and traceable.

(1) The paper records (notebook, recording paper) are under controlled management, and reforms are under version control. The modification of the record keeps the initial record clear and discernible, indicates name of the modifier, modification date and reason.

(2) Electronic data collection system passes the system verification, and retains verification record. Set user management, role management and permission management for the computerized system, different personnel or roles have the unique logon rights.

2. Enable and store the audit track and instrument diary of the computerized system, the laboratory shall specify the storage time limit.

3. Physical environment for records storage and backup shall be temperature and humidity monitored, and equipped with equipment for fireproof, waterproof, heat proof, moisture proof, disruption resistant, and theft proof. There shall be limitation, recording and monitoring of person in contact with the carrier of the record storage and backup.

4. The records are timely archived after the project finished, and are specially managed by the designated person. Timely record the circumstances of archiving, referring, borrowing and return. The archives room is equipped with necessary equipment for theft proof, fireproof, water proof, insect proof and antimagnetic, and be regularly maintained and inspected.

**IV. Determination Principles for Inspection Results**

(I) After checking the original record and data of the study process, confirm on-site, and confirm through inspection, if any of the following circumstances is identified, the inspection is determined as "Fail":

1. Fabricate or ungrounded modify subject information, test data, test record, and information of test drug;

2. Use the reference preparation substitute for the test preparation, use the test preparation substitute for the reference preparation or use product purchased in the market substitute for self-developed investigational drug, or otherwise use false investigational drugs;

3. Withhold test data, ungrounded discard test data, or otherwise violate the trial protocol and use test data selectively;

4. Hide doubted and unanticipated serious adverse reaction;

5. Hide concomitant drugs prohibited by the trial protocol;

6. Intentionally destroy and hide test data or data storage media;

7. The key study activities and data cannot be traced;

8. The application dossier is inconsistent with the original record, and has an impact on the result evaluation;

9. Other serious problem of data reliability;

10. Refuse or fail to cooperate with the inspection, resulting in the inability to continue on-site inspection;

11. Other circumstances that defined by laws and regulations that shall be deemed “Fail”.

(II) After checking the original record and data of the study process, confirm on-site, and confirm through inspection, if there is no problem identified or the problem identified does not constitute the circumstances mentioned above, the inspection is determined as "Pass". Among which, the identified problem may have impact on data quality and reliability, which needs special attention in the review.