**Key Points and Determination Principles of**

**Drug Registration Inspection**

**(Pharmacological and Toxicological Study)**

**(Trial)**

In order to ensure the quality of drug registration inspection and to unify the scope of inspection and determination standards, in accordance with the *Drug Administration Law of the People's Republic of China*, *Measures for Administration of Drug Registration* and other laws and regulations and related guidelines, the *Key Points and Determination Principles of Drug Registration Inspection (Pharmacological and Toxicological study) (Trial)* is hereby formulated.

**I. purpose**

The purpose of on-site inspection of Pharmacological and Toxicological study is to check the compliance of Pharmacological and Toxicological study and verify the authenticity and consistency of relevant application dossiers through the inspection and / or on-site confirmation of the data integrity of the original data of Pharmacological and Toxicological study.

**II. Scope**

(I) It is applicable to the on-site inspection of Pharmacological and Toxicological study in the research and development (R&D) on-site inspection of drug registration initiated by the Center for Drug Evaluation (CDE) of the National Medical Products Administration (NMPA) and organized and implemented by the Center for Food and Drug Inspection (CFDI) of NMPA.

(II) On-site inspection of Pharmacological and Toxicological study is mainly to inspect the study conditions of Pharmacological and Toxicological, including study conditions, protocol implementation, data records and result reports. Based on registration requirements and risk principles, only part of the content of some Pharmacological and Toxicological trial items can be inspected.

**III. Key Points of On-site Inspection**

**(I) Testing facility and personnel**

1. The name of the testing facility, the address of the testing facility site and the content of the study carried out should be consistent with that in the application dossiers; for a multi-site study, all testing facilities involved and their responsibilities performed should be fully and accurately reported in the application dossiers;

2. Non-clinical safety studies should be conducted by a testing facility which has been granted a Good Laboratory Practice (GLP) Certificate by the national drug regulatory authority, and the studies conducted should be within the scope of the studies specified in the GLP Certificate;

3. When radioactive and biohazardous substances are used in the study, the testing facility should provide the corresponding documentation for fulfilling the requirements of the relevant national regulations;

4. The contracted study should be evidenced as such with the supporting documentation.;

5. There should be established standard operating procedures (SOPs) or other operational instructions in place for the study conducted;

6. The study personnel should be of adequate knowledge, qualifications, working experience and training to perform their duties in the study, and the personnel files of those who play important roles in the study should be retained completely; the personnel involved in the study should be consistent with that specified in the application dossiers.

**(II) Facilities**

1. There should be appropriate facilities for carrying out the study with proper design and good maintenance;

2. In case of laboratory animals used in a study, there should be proper animal facilities for carrying out the study with the corresponding approval documentation for the use of laboratory animals; records of environmental monitoring of animal facilities and handling of unexpected events in the course of the study should be retained completely;

3. The storage conditions of the test/control articles and their formulations, biological samples, study files and specimens, etc. should be in conformity with those specified in the study protocol, SOPs or other operational instructions; records of corresponding environmental monitoring and handling of unexpected events in the course of the study should be retained completely.

**(III) Instruments and equipment**

1. There should be appropriate instruments and equipment with adequate capacity for carrying out the study;

2. Records of use, cleaning, maintenance, testing, calibration, verification or validation, repair, handling of unexpected events and decommission of instruments and equipment used in the study during the study period should be retained completely; the testing time and items in the use records of instruments and equipment should be in line with that as required by the study;

3. Computerized systems (or equipment and instruments interface to a computer) applied to data acquisition, transmission, storage, processing, archiving, etc., should be validated properly, and the corresponding validation plans, records and reports should be maintained; when hardware or software replaced, upgraded or patched, the system should be evaluated and relevant evaluation reports should be kept; if an additional validation needed after evaluation, the relevant validation plans, records and reports should be kept;

4. The electronic audit trail feature (when present) should be turned on; the electronic data generated should be with the complete audit trail and electronic signature to ensure its authenticity and traceability; access to the computerized system should be properly authorized and controlled.

5. Study data generated by the computerized system should be backed up at an adequate frequency and preserved properly to ensure data completeness and traceability.

**(IV) Test/control articles**

1. The receipt, storage, distribution, use, reserve samples, return or disposal of the test/control articles should be recorded completely and their accountability should be maintained;

2. The storage conditions of the test/control articles should be in conformity with those specified in the study protocol or other supporting documents (such as instructions for use, certificates of analysis, etc.); records of monitoring storage conditions and handling unexpected events of the test/control articles and their formulations during the study period should be retained completely;

3. Records of formulating the test/control articles, storage and use of their formulations, and the residuals for disposal should be retained completely; the amount of each requisition should be in line with that in dispensing record of the test articles, and the amount of formulating, use and residual for disposal should be in reconciliation;

4. Records of formulating, storage, use, return and disposal of narcotic drugs and modeling reagents (drugs) used in the study should be retained completely.

**(V) Test systems**

1. Laboratory animals as test systems

(1) The source of laboratory animals used in the study should be clear and compliant with the related regulations. Suppliers should have corresponding qualification as required for manufacture or supply of laboratory animals; the guarantee certificate or other relevant documentation for the quality of laboratory animals should be maintained completely;

(2) The information on laboratory animals such as species, quantity, age, gender, body weight range, grade and so forth should be consistent with that specified in the application dossiers;

(3) There should be an appropriate individual identification for each of laboratory animals to ensure traceability in the course of the study;

(4) Records of receipt, quarantine, use and disposal of laboratory animals should be retained completely, and the quantity shall be accountable and consistent with that specified in the application dossiers;

(5) The name, source, batch number (if applicable), expiration date, sample testing items and results of feed, bedding and drinking water for laboratory animals should be consistent with that described in the application dossiers and with that in testing reports retained in the study files;

2. Test systems other than laboratory animals

(1) The source of the test system used in the study should be clear and compliant with the related regulation, and the relevant supporting documentation for acquisition and characterization of the test system should be kept completely; documentation for assessing suitability of the test system should be kept completely.

(2) Records of storage, use, and passage, etc. of test system should be retained completely, and information such as time, quantity, and so forth in the records should be consistent with that specified in the application dossiers.

**(VI) Biological samples**

Records of collection, labelling, transportation, storage, transfer, processing, analysis and testing, etc. of biological samples should be retained in a complete and traceable manner.

**(VII) Original records**

1. The consistency of the application dossiers with the study protocol, raw data and final report should be audited;

2. All original records should be recorded truthfully, promptly, accurately, completely and traceably, and the results should be consistent with those in the application dossiers; the changes made in the records should not obscure the original entry, and the person who made the change should sign and date with the reason for change;

3. Data re-testing should be carried out in accordance with the corresponding SOPs or the operational instructions, and the reason for re-testing should be recorded; results of each batch of re-testing and the reason for selecting the result to include in the final report should be retained;

4. According to the inspection task, the representative samples of the raw data from processes of the study should be taken for audit to verify consistency with the application dossiers. The samples taken for audit generally include but are not limited to:

(1) Records of receipt, grouping designation, administration, testing and evaluation, and disposal of test system should be retained completely and traceably, and should be consistent with those in the application dossiers. For example:

Records of animal body weight should be complete;

Records of animal food and water consumption records should be complete;

Records of animal observation, administration, physiological and biochemical testing should be complete;

Records of animal anesthesia, euthanasia, and necropsy should be complete;

Records of recovery, passage, incubation, processing and administration of non-animal test system such as cells should be complete;

(2) Records of receipt, formulating, analysis (such as homogeneity, concentration, stability, etc.), use and return of the test/control articles should be retained completely and traceably and should be consistent with those in the application dossiers. For example:

Records of the test/control articles on stability, batch number, purity, specification, quantity, physical and chemical characteristics, storage conditions, expiration date, etc. should be retained completely;

Records of formulating, distribution, and return, etc. of the test/control articles should be complete;

(3) Records of biological samples (such as blood, urine, tissue, etc.) on collection (such as collection time, etc.), labelling, processing, transfer, testing and storage should be retained in a complete and traceable manner and should be consistent with those in the application dossiers. For example:

Records of transfer and records of temperature monitoring during transportation should be retained completely;

Records of development and validation of analytical methods for testing test/control articles in vehicle and blood samples should be retained completely;

To sample and audit the pharmacokinetic (toxicokinetic) data, including chromatograms and analytical data, for the purpose of verifying consistency with those submitted in the application;

Pathological examination records (such as anatomy, tissue collection, pathological section preparation and histopathological evaluation records, etc.) should be retained completely;

5. Deviations from study protocol, SOPs or other operational instructions should be recorded, and evaluated in a timely manner, and reported truthfully in the final report.

**(Ⅷ) Others**

1. The applicant and the testing facility under inspection should ensure that the original study materials retained are complete and can be provided for inspection in a timely manner, including an original copy of protocol, raw data, specimens, relevant testing reports, reserve samples of test/control articles, an original copy of the final study report and other documentation related to the study;

2. The applicant and the testing facility under inspection should actively cooperate with inspection and should not obstruct or interfere with inspection.

**IV. Determination Principle of Inspection Results**

(I) The original records and data in the study process shall be inspected and confirmed on the spot. If one of the following circumstances is found after inspection, the inspection shall be deemed as "failed”:

1. Fabricating or modifying the information of the test system, study data, study records, test/control articles without reasonable explanation;

2. Using false test/control articles;

3. Concealing the study data, discard the study data without a reasonable explanation, or use the study data selectively in violation of the study protocol in other ways;

4. Intentionally destroying or concealing study data or data storage medium;

5. Key study activities and data cannot be traced;

6. The application dossiers are inconsistent with the original records and affect the evaluation results;

7. Other serious data integrity problems;

8. Refusing or refusing to cooperate with the inspection, causing the discontinuation of on-site inspection;

9. Other circumstances that should not be passed as prescribed by laws and regulations.

(II) The original records and data in the study process are inspected and confirmed on the spot. If no problems are found or the problems found do not constitute the above failure situation, the inspection shall be deemed as "passed". Among them, the problems that may have an impact on the quality and reliability of the data need to be reviewed and focused on.