**Key Points and Determination Principles of**

 **Drug Registration Inspection**

**(Pharmaceutical Development and Manufacturing Site)**

**(Trial)**

To ensure the quality of drug registration inspection and unify the scope of inspection and determination standards, in accordance with the *Drug Administration Law of the People's Republic of China, the Drug Registration Regulation* and other laws and regulations and related guidelines, the *Key Points and Determination Principles of Drug Registration Inspection (Pharmaceutical Development and Manufacturing Site)* (Trial) is hereby formulated.

**I. Purpose**

(I) The purpose of on-site inspection of pharmaceutical development (hereinafter referred to as Development Site Inspection) is mainly to verify the authenticity and consistency of the relevant application dossiers through the inspection and / or on-site confirmation of the data integrity of the pharmaceutical Development (including formulation and process study, trial sample production, quality control study, stability study, etc.).

(II) The purpose of drug registration inspection of manufacturing site (hereinafter referred to as Manufacturing Site Inspection) is mainly to verify the authenticity of the application dossiers and to verify the consistency of the relevant production and quality control activities with the application dossiers (such as formulations, production processes, specifications, key facilities and equipment, etc.) and commercial production conditions under the commercial production scale through on-site inspection of the commercial production conditions and capabilities of the proposed species, and the reliability of the data.

**II. Scope**

(I) It is applicable to the development site inspection and manufacturing site inspection 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 (CDFI) of NMPA. Based on registration requirements and risk principles, the development site inspection and the manufacturing site inspection can be conducted only for key sites undertaking main study tasks, or only for parts of some key points.

(II) In general, Development Site Inspection starts with the manufacture of confirmatory clinical trials, bioequivalence studies and other drug clinical trials related batches, by the commercial-scale production process validation batches. It is focusing on the key clinical batches that affect drug quality evaluation, such as confirmatory clinical trial batches/bioequivalence study batches, technology transfer batches, stability test batches involved in the application dossiers, and others. When necessary, it can be traced back to study content such as project initiation, formulation screening, and process optimization.

If the drug clinical trial is exempted, the relevant batch for quality comparability study shall be taken as the starting point; if no quality comparability study is conducted, the batch after the process and the formulation are basically determined shall be taken as the starting point.

(III) In general, the manufacturing site inspection is based on the knowledge acquired through technology transfer, starting from commercial-scale production process validation batches to the on-site dynamic production batches, with focus on commercial-scale production process validation batches and dynamic production batches and related changes, stability study and other study and pilot batches during this period.

(IV) If need, extended inspection shall be carried out on manufacturers, suppliers of chemical API, traditional Chinese medicine (TCM) materials, TCM decoction pieces and extracts, excipients, and packaging materials and containers that directly contact the drugs or other entrusted institutions by referring to the Key Points and Determination Principles.

**III. Key Points for Development Site Inspection**

(I) Quality management

To carry out drug study, an organizational structure and quality management system suitable for the study content should be established, personnel, facilities, equipment, instruments, etc. suitable for the drug study content should be provided, and corresponding management systems or standard operating procedures (SOPs) should be formulated and implemented.

1. Organization and personnel

The management organization suitable for the study content should be established to carry out corresponding quality management.

The study and management personnel with appropriate qualifications (including academic qualifications, training, or practical experience) shall be equipped to comply with the provisions of relevant national laws and regulations and ensure the authenticity and reliability of trial data and dossiers.

2. Study conditions

The sites, facilities, equipment, instruments and management systems or SOPs that are suitable for the study and determined according to different stages of development and risks shall be provided, which shall be consistent with study records and application dossiers.

3. Documents and records

The management system or SOPs for documents and records should be established. The entire process of drug development should have corresponding records, including data and records of pilot and exploratory studies.

4. Change management and deviation handling

Management systems or SOPs for changes, deviations and study failures etc. should be established at least once the drug start the clinical trial phase and they shall be suitable for the drug development phase. Deviations of key batches or study failures should be appropriately investigated and/or analyzed and recorded.

5. Contract study

Where other institutions are contracted with part or all the pharmaceutical development and pilot production, the contract giver shall evaluate the study capacity and quality management system of the contract acceptor to confirm its study conditions and study situation. The two parties should sign an entrustment contract or other effective agreement to clearly stipulate the responsibilities of each party, the content of the study and related technical matters. The contract giver shall be responsible for the process and results of the contract study and ensure the data integrity in the contract study. The contract acceptor shall comply with relevant requirements and ensure that the study and sample preparation process is standardized, the data are true and reliable, and the development process can be traced.

(II) Formulation and process

The formulation and process study should be scientific sound and reasonably designed, and the relevant study records should be true and complete and consistent with the application dossiers.

1. The formula composition, process flow diagram, process description, key process parameters and scope determined by the study should be consistent with the application dossiers.

2. The test data and time determined by the study of the formulation process should be consistent with the application dossiers.

(III) Pilot production

1. The pilot production records, especially the pilot production records of key batch, should be kept complete.

2. The formulation and production process, in-process control, pilot production site and production line, the main production equipment model used, process parameters and original records of the key batches should be consistent with the application dossiers.

3. There should be a reconciliation of the batch quantity of the pilot production, remaining quantity and used quantity. The actual products of pilot-production should be retained, and the key batches produced after the formulation process is determined shall not be destructed before the marketing application is approved.

4. The production of relevant batches used for confirmatory phase of clinical trials, bioequivalence studies etc. drug clinical trials should meet the relevant requirements of the corresponding Good Manufacturing Practice (GMP).

(IV) APIs, pharmaceutical excipients and packaging materials and containers in direct contact with drugs

1. The APIs and pharmaceutical excipients used in the pilot production of key batches, packaging materials and containers in direct contact with the drugs shall have legal sources (such as supply agreements, invoices, etc.), and the relevant information should be consistent with the application dossiers.

The source of bacterial strains, cell strains, and plasma shall be legal, clear, and traceable, and consistent with the application dossiers.

The origin, place of production and processing methods of the TCM decoction pieces shall be clearly defined and shall be consistent with the application dossiers.

2. The time and the quantity of APIs and pharmaceutical excipients, TCM decoction pieces and extracts, packaging materials and containers that directly contact drugs, etc. should be matched with the production situation.

The establishment, testing, and release of seed batches and cell banks of all levels of bacteria and viruses etc. shall meet the requirements of the application dossiers.

3. The internal control specification to APIs and pharmaceutical excipients, packaging materials and containers that are in direct contact with drugs should be established in accordance with the characteristics of the formulation, and the corresponding study process shall be consistent with the application dossiers.

4. The APIs and pharmaceutical excipients used in the pilot production of the key batches and the packaging materials and containers that directly contact the drugs should have a test report and be consistent with the application dossiers.

(V) Quality control

1. The instruments and equipment used in the key batch study shall be subject to the necessary validation or calibration, and have use records, maintenance records and validation or calibration records, which correspond to the study time, and the content of the records are consistent with the application dossiers.

2. The batches used for quality study, study time and pilot batch production time should be able to correspond.

3. The original records and experimental atlas data of all quality study projects, such as dissolution/release test, relevant substances, assay/potency and other key quality attribute studies and experiment method, should be complete, reliable, and traceable, and the data format should match the instruments and equipment used.

(VI) Technology transfer

The technology transfer from the drug development to the production stage is a systematic engineering, whose purpose is to transfer the product knowledge and experience acquired during the development site to the production enterprise. The production enterprise that accepts the technology transfer shall have the ability to implement the transferred technology and produce drugs that meet the registration application.

1. Technology transfer should complete the transfer of technical documents and have corresponding key documents and records.

2. The personnel, equipment, process, materials, and other factors involved in the technology transfer should be evaluated, and corresponding measures should be taken during the technology transfer to reduce risks.

3. After technology transfer or scale-up, commercial-scale production process validation should be completed, and the validation data should be able to support the critical process parameters of commercial batch size production.

4. The transfer of analytical methods should be qualified, recorded and reported.

(VII) reference substance and reference listed drug

1. The reference/standard substance used shall have a legal source certificate, and be used within the validity period, and consistent with the application dossiers. If it is a working standard, there should be a complete standardization record and it should be used within the validity period; there should be records or evidence of receipt, distribution and use of the reference /standard substance, which should be consistent with the actual study/evaluation work.

2. The reference listed drug used should be consistent with the application dossiers, with clear source and proof of origin, such as purchase invoice, gift certificate, etc.; package labels, instructions for use and remaining quantity of reference listed drug shall be provided; records or certificates of receipt, distribution and use of reference listed drug shall be consistent with the actual study/evaluation work.

3. The reference substance/reference listed drug should be stored in accordance with its prescribed storage conditions and consistent with the application dossiers.

(VIII) Stability study

Enterprises should make a stability study protocol and carry out study in accordance with the stability study protocol. The batch of stability study should be consistent with the application dossiers.

1. The packaging materials and containers used in the stability study samples that directly contact the drug should be consistent with the application dossiers.

2. The storage conditions of the stability study samples, etc., should be consistent with the application dossiers.

3. The raw test data recorded at each time point in the stability study should be consistent with the application dossiers.

4. The data involved in the stability study should be traceable, complete, and reliable.

(IX) Data integrity

The data in the application dossiers shall be true, accurate and traceable, and the relevant original records, original atlas and original data shall be consistent with the application dossiers. The Development site shall take effective measures to prevent the modification, deletion and coverage of data to ensure the data integrity. Among them, method validation and subsequent study data that affect product quality and stability data evaluation are particularly important.

1. Data (including test atlas) in quality and stability studies shall be traceable: Infrared spectroscopy, ultraviolet-visible spectrophotometry, high performance or ultra-high performance liquid chromatography, gas chromatography and so on are used to obtain the atlas printed with a digital signal processing system; there should be traceable key information (storage path of the atlas data file, data collection date, acquisition method parameters, etc.), and the electronic version of each atlas should be kept complete; the weighing and printing records of electronic balances should be traceable; certain items that require visual test (such as those using thin-layer chromatography, paper chromatography, electrophoresis, etc.) should have electronic files obtained from photos or digital photography.

2. During the drug development phase, the equipment with digital signal processing system should enable the audit trail function, and the data to be inspected should be in the computer or database where the data are collected. The audit trail function should be able to display all changes to the previously retained data and raw data, and link to the data modifier, and record the time of change and the reason for the change; and the user should not have the authority to modify or close the audit trail function.

3. The paper atlas code/test sample code should correspond to the original record and be traceable.

4. The electronic atlas should be a continuous sequence. If there is a selection or abandonment of the atlas, the corresponding explanation or justification should be provided.

5. The data should be attributable to specific operators. For lab equipment with a computerized system, each user should set an independent account and password, or use other methods to ensure that the data can be attributable to specific operators.

**IV. Determination Principles of Development Site Inspection Results**

(I) The original records and data of development are verified and/or confirmed on the spot. If one of the following situations is found through inspection, the inspection shall be deemed "failed".

1. Fabricating or modifying study data and records without reasonable explanation;

2. Replacing developed drugs with reference listed drugs, replacing reference listed drugs with developed drugs or replacing self-developed drugs with the drugs purchased from the market, or otherwise use fake drugs in pharmaceutical development;

3. Concealing development data, discarding data without a reasonable explanation, or selectively using data in other ways, resulting in an impact on drug quality evaluation;

4. Intentionally destroying, concealing development data or data storage media, etc., intentionally destroying the authenticity of development data;

5. Being inconsistent with the application dossiers and may have a greater impact on the drug quality evaluation;

6. There are serious data integrity problems. The lack of original records of key study activities and data makes it impossible to trace the source, which has an impact on the evaluation of drug safety, effectiveness, and quality controllability;

7. Refusing or not cooperate with the inspection, causing the discontinuation of on-site inspection;

8. Other circumstances stipulated by laws and regulations that should not be passed.

(II) The original records and data in the development are verified and/or confirmed on the spot. If no authenticity problems of the application dossiers are found, and the problems found do not constitute the above-mentioned failure conditions, the inspection shall be deemed as "passed". Among them, if some non-critical information in the application dossiers is found to be inconsistent or data integrity problems are found but may not affect the evaluation of drug safety, effectiveness, and quality controllability, it shall be paid special attention in the review process.

**V. Key Points for Manufacturing site Inspection**

(I) Quality management

Drug production enterprises should have a quality system that covers all factors that affect the quality of drugs, have an organization suitable for drug production, and establish a quality assurance system to ensure the effective operation of the quality system.

1. Quality management should cover all factors that affect the quality of drugs, ensure that the products produced meet the proposed process and quality requirements, and minimize the risks of contamination, cross-contamination, mix-up, and errors in the drug production process.

2. The senior management personnel of the enterprise shall ensure the achievement of the established quality objectives and provide sufficient and qualified personnel, premises, facilities, and equipment to achieve the quality objectives.

3. The enterprise should establish a management organization suitable for drug production, clarify the responsibilities of each department, and ensure that the technology transfer is reasonable and traceable.

4. The enterprise should be equipped with enough management and operation personnel with appropriate qualifications. Key personnel and personnel in key positions shall be trained and understand the knowledge of this product, and personnel in key positions must be familiar with the key quality control and key production operation requirements of this product.

5. The enterprise shall establish management documents that meet the production quality requirements of this product, including product technology transfer management documents, related production quality documents of GMP, and product R&D files management documents, etc.

6. The enterprise shall establish the relevant management standard operating procedures for change control, deviation, supplier management, and handling of out of specification test results in accordance with the requirements of the GMP and implement them in accordance with the regulations. The adopted methods, measures, forms, and formulated documents should be suitable with the corresponding drug life cycle.

7. The enterprise should establish a quality risk management system to evaluate quality risks based on scientific knowledge and experience to ensure product quality.

(II) Premises and facilities and equipment

The premises, facilities, and key production equipment of the enterprise shall be consistent with the registration application dossiers and be matched with the production of commercial batch size. The measures to prevent contamination and cross-contamination during the drug production process shall be effective.

1. The production premises and facilities, storage conditions, etc. should meet the requirements for commercial batch size production, and the production capacity of key production equipment should be matched with the commercial batch size production.

2. To satisfy the production of new varieties for registration application, the original premises, facilities and equipment should be evaluated, and corresponding changes should be made when necessary. If it is a newly built enterprise or workshop, when commercial-scale production process is validated, the premises and facilities related to production, and key production equipment are subject to qualification, including design qualification, installation qualification, operation qualification and performance qualification.

3. For non-dedicated production lines, the rationality of collinear varieties should be evaluated, the risk of contamination and cross-contamination caused by collinear production should be evaluated, and effective measures to prevent contamination and cross-contamination should be taken; an effective cleaning procedure should be established and validated, and the establishment of the limit for its active substance residue should be based on the evaluation of toxicological trial data or toxicological literature dossiers.

(III) Materials

In relation to the entire process of procurement, reception, storage, testing, release, distribution, use, return, and destruction of related materials, it should be ensured that the materials are free from contamination, cross-contamination, mix-up, and errors during the above-mentioned process.

1. The APIs and pharmaceutical excipients/critical materials needed in the production (including bacterial strains, cells, plasma, adjuvants, culture media, etc. used in biological products) and packaging materials should have corresponding management systems and be complied with.

2. The suppliers of APIs and pharmaceutical excipients used in product production, packaging materials and containers that directly contact drugs shall be audited and managed according to management procedures.

3. The quality specification, manufacturers/sources of the APIs and pharmaceutical excipients and packaging materials and containers that directly contact the drugs shall be consistent with the registration application dossiers, sampling and tests shall be carried out in accordance with the relevant SOPs, and a full test report shall be issued.

The establishment, test, and release of seed batches and cell banks of all levels of bacteria and virus seeds shall meet the requirements of the application dossiers.

4. The APIs and pharmaceutical excipients and the packaging materials and containers that directly contact the drugs shall be stored, used, and managed in accordance with the corresponding requirements, and a reasonable storage period shall be established.

(IV) Batch production

Starting with commercial-scale production process validation, the consistency of the enterprise's production process with the registration dossiers, and the ability to consistently and stably produce products that meet the registration application shall be confirmed.

1. The formulation, batch size, actual production process, and batch production records of key batches such as commercial-scale production process validation batches and on-site inspection dynamic production batches (if any) should be consistent with the process procedure/manufacturing and testing procedures and the registration application.

Commercial-scale production process validation data should support the critical process parameters of batch production and be within the specified range. If there are other pilot batches than commercial-scale production process validation batches, the historical production process data of the product and the quality related to the product should be traceable.

2. Batch production records, equipment using records, material consuming records, test records and other records should be consistent and traceable.

3. The pre-handling and processing methods of TCM materials should be consistent with the application dossiers and be specified in the product process regulations. For purchased decoction pieces, the quality agreement should specify the pre-handling and processing requirements.

(V) Quality control

The personnel, facilities, and equipment of the quality control laboratory should be suitable with product quality control and should be equipped with necessary reference books such as pharmacopoeias and standard atlases, as well as corresponding standard substances or reference substance and other related standard materials. The enterprise shall establish a corresponding quality control system, conduct sampling and tests in accordance with the requirements of the GMP, and obtain true and reliable test results.

1. Testing facilities, equipment and instruments shall be validated or calibrated, and the use records shall be traceable within the validity period.

2. Samples, standard materials, reagents, bacteria strain, etc. should be managed and used in accordance with regulations.

3. The specifications of samples, intermediate products/intermediates and key materials should be consistent with the proposed specification, and tests should be carried out as required. The test method shall be methodologically validated or confirmed in accordance with the regulations.

4. The product should be tested for stability in accordance with regulations; intermediate products/intermediates with shelf life should also be studied if necessary.

5. If there is a contract test, both parties should sign a contract or agreement, and the contract giver should conduct an audit to ensure that the data provided by the entrusted party are reliable.

(VI) Data integrity

The enterprise should take effective measures to prevent data modification, deletion, overwriting, etc., to ensure data integrity. The data in the application dossiers shall be true, accurate and traceable, and the relevant original records, original atlases, and original data shall be consistent with the application dossiers. Among them, production, and test data such as commercial-scale production process validation and stability testing are particularly important.

1. The relevant original records, especially the electronic raw data, should be consistent with the paper data in the application dossiers. The data should be clear, readable, lucid, and traceable, and data preservation should ensure that the steps and sequence of data generation can be fully reproduced.

2. According to the signature in the production, testing or other related records, it can be traced back to the creator, modifier, and other operators of the data.

3. The computerized system used in production and testing should be validated, and the hierarchical management and access of related users should be set up reasonably.

4. A data audit trail system should be used to ensure the reliability of the data in the generation of key data of the key batch. For instruments and equipment that does not have an audit trail function, adequate measures should be taken to ensure the reliability of its data.

5. For quality study items, such as the original records, experimental atlases, and experimental methodological investigations of critical quality attribute studies such as dissolution/release, related substances, assay/potency, etc., the original data should be complete and reliable, and the data format should match the instruments and equipment used.

**VI. Determination Principles of Manufacturing Site Results**

(I) After on-site confirmation of the production process and commercial production conditions, as well as the verification of the original records and data in the production, if one of the following situations is found through inspection, the inspection shall be deemed as "failed":

1. There are serious deviations from relevant laws and regulations such as Good Manufacturing Practice (GMP), which may bring serious risks to product quality or cause harm to users;

2. Fabricating production and test records and data;

3. Concealing records and data, discarding records and data without a reasonable explanation, or selectively using records and data in other ways leads to an impact on drug quality evaluation;

4. Intentionally destroying, concealing records and data, or its storage media, etc., intentionally destroying the authenticity of records and data;

5. It is impossible to prove that it can achieve consistent and stable production in accordance with the proposed commercial production conditions for marketing;

6. There are serious data integrity problems, and key data and records cannot be traced, which has an impact on the evaluation of drug quality;

7. Refusing or not cooperate with the inspection, causing the discontinuation of on-site inspection;

8. Other circumstances stipulated by laws and regulations that should not be passed.

(II) After on-site confirmation of the production process and conditions, as well as the verification of the original records and data during the production process, if no problem with the authenticity of the application dossiers is found, the conditions for commercial production of the drug are available, and the problems found do not constitute the above failure, the inspection shall be deem as "passed". Among them, if it is found that there is inconsistency with the application dossiers or data integrity problems but may not affect the quality evaluation of the drug, or the commercial production conditions for the drug are basically available but still need to be further improved, it shall be paid special attention in the review process.