**Work Procedures for Drug Registration Inspection**

 **(Trial)**

**Chapter I General**

**Article 1** In order to standardize the work process of drug registration inspection (hereinafter referred to as registration inspection), strengthen the connection between registration inspection and evaluation, and ensure the quality and efficiency of registration inspection, the Procedures is formulated in accordance with the *Drug Registration* *Regulation* and *Drug Manufacture Regulation*.

**Article 2** This Procedure is applicable to the domestic registration inspection of drug development site and manufacturing site organized by the National Medical Products Administration (NMPA). The Center for Food and Drug Inspection of NMPA (hereinafter referred to as CFDI) organizes the implementation of registration inspection work.

**Article 3** Registration inspection is the inspection activity initiated by the Center for Drug Evaluation of NMPA (hereinafter referred to as CDE) to verify the authenticity and consistency of the drug registration application dossiers, and the commercial production conditions of the drug ,check the compliance, data integrity, etc. on the development site and manufacturing site focusing on the development and manufacturing involved in the application dossiers of relevant registration applications; and, if necessary, extended inspection activities may be carried out to the manufacturers, suppliers or other contracted institutions of chemical active pharmaceutical ingredient, traditional Chinese medicine (TCM) materials, TCM decoction pieces and extracts, excipients, and packaging materials and containers that directly contact the drugs involved in drug registration applications.

Registration inspection is divided into the registration on-site inspection of pharmaceutical development (hereinafter referred to as Development Site Inspection) and the drug registration inspection of manufacturing site (hereinafter referred to as Manufacturing Site Inspection).

**Article 4** Development Site Inspection is to check the compliance and data integrity of drug development, verify the development of drug registration application, and review the original records and data to confirm the authenticity and consistency of application dossiers. Development Site Inspection includes on-site inspection of Chemical Manufacturing and Control (hereinafter referred to as CMC) development, on-site inspection of Pharmacological and Toxicological study, and on-site inspection of drug clinical trials.

The on-site inspection of CMC development is mainly to inspect the original data, records, including pharmaceutical formulation and process study, trial sample manufacturing, quality control study and stability study etc. development activities, and on-site inspection.

The on-site inspection of Pharmacological and Toxicological study is mainly to inspect the Pharmacological and Toxicological study, including the conditions of pharmacology and/or toxicology study, protocol implementation situation, data records and result reports etc.

The on-site inspection of drug clinical trials is mainly to check the registration application dossiers and the original records and documents of clinical trials, evaluate whether the implementation of the trial, data records and result reports comply with the trial protocol and relevant laws and regulations of drug clinical trials, and pay attention to the protection of subjects. If necessary, random sample and test can be conducted on drugs used in clinical trials.

**Article 5** Manufacturing Site Inspection is the process of verifying the commercial scale production process validation and pilot production process applied for drug registration, and confirming whether it compliance to the proposed or approved source of raw materials, excipients and packaging materials, formulation, production process, test method and quality specification, stability study, etc. , and the data integrity of relevant commercial scale production process, and whether it is qualified for commercial production.

**Article 6** The applicant for drug registration (hereinafter referred to as the applicant) shall ensure that the information in the entire process of development and registration activities is true, accurate, complete, and traceable, and shall provide true, sufficient, and reliable data and samples when file an application for drug marketing authorization and shall possess the conditions for commercial production of drugs marketing. The applicant and the inspected institution shall cooperate with the registration inspection work.

**Article 7** Inspectors shall inspect the registration development and manufacturing of related varieties of the inspected institution in accordance with the law.

Inspectors shall strictly abide by national laws, regulations, and work disciplines, have no conflicts of interest with the applicant and the inspected institution, earnestly perform their duties during the inspection, and conduct registration inspections impartially and honestly. The dossiers and information provided by the applicant and the inspected institution shall be kept confidential.

**Chapter II Basic Requirements for Registration Inspection**

**Article 8** Registration inspection shall follow the principles of openness, fairness, and justice, and be guided by clinical value or problems to promote the drug development and approval.

**Article 9** CFDI and the institutions of drug evaluation, drug testing and others shall establish a joint mechanism for registration inspection, evaluation, and registration test, and strengthen communication, exchanges, and coordination to research and solve problems in the registration inspection work.

During the organization and implementation of the registration inspection, CFDI can communicate and adjust the inspection object, inspection content, and inspection focus with CDE. Under special circumstances, based on the risk assessment analysis, CFDI may provide an opinion on whether to conduct on-site inspection to CDE.

**Article 10** CFDI shall establish a quality management system related to registration inspection, formulate standard operating procedures for registration inspection and the corresponding *Key Points and Determination Principles of Drug Registration Inspection*, strengthen the construction of the inspector team, establish a registration inspection inspector database, and regulate the related work of registration inspection.

**Article 11** CFDI shall carry out drug registration inspection according to the inspection tasks initiated by CDE and clarify the content of the inspection in combination with the characteristics of the variety, the characteristics and risks of the inspected institutions, the requirements of whether to start Dynamic Manufacturing Site Inspection proposed by CDE, and the content of the inspection concerns and the other factors and shall adopt the form of on-site inspection or data inspection. Usually, on-site inspection is carried out for the commercial production conditions of the varieties. If necessary, dynamic inspection can be carried out during the on-site inspection according to the needs of the registration work.

Caused-related inspections are generally carried out around the reasons for the start-up of the inspection.

CFDI may require the applicant to submit relevant dossiers to CFDI before the inspection for the purpose of studying and determining the mode and method of the inspection organization according to the needs of the work.

**Article 12** If the drug regulatory authorities of a province, autonomous region, or municipality directly under the Central Government determine that it is necessary to conduct Pre-market inspection of Good Manufacturing Practice of Medical Products (GMP) during the Manufacturing Site Inspection period, CFDI shall coordinate the drug regulatory authorities of the relevant province, autonomous region, or municipality directly under the Central Government to implement the inspection simultaneously with Manufacturing Site Inspection.

**Article 13** The inspection report and inspection results are only for the scope and content of the inspection of the registration application, and do not cover all the registration application dossiers of the registration application and the evaluation of related development activities.

**Article 14** Priority shall be given to registration inspection of the drugs in special approval procedures and priority evaluation and approval procedures.

**Article 15** CFDI shall disclose the registration inspection process to applicants and provide information such as the progress and conclusions of the registration inspection work that can be inquired.

CFDI shall feedback the problems found in the registration inspection to the drug regulatory authorities of the province, autonomous region, or municipality directly under the Central Government where the applicant and the inspected institution are located.

**Article 16** Before the registration inspection, the applicant can communicate with CFDI on major matters. During the registration inspection period, CFDI can communicate with applicants if needs.

**Article 17** CFDI shall establish an expert consultation system if needs and seek for expert opinions on major and difficult issues during the registration inspection process.

**Article 18** CFDI explores the establishment of a caused-related registration inspection model based on information such as the drug product archives and institutional files of the NMPA; explores the application of off-site inspection methods based on the development of information management methods; continues to improve the system of technical guidelines for inspection.

**Chapter III Basic Procedures for Registration Inspection**

Section 1 Inspection tasks initiation

**Article 19** CFDI accepts the registration inspection tasks which initiated by CDE. Then, CFDI should confirm and verify the registration inspection tasks and the attached registration inspection dossiers.

Those with clear targets, clear start-up conclusions, clear focus points (if any), and complete information related to the focus points shall be accepted.

If the registration inspection task could not meet the acceptance conditions, it shall be improved by CDE, and accepted by CFDI after meeting the acceptance conditions.

**Article 20** For received registration inspection tasks, CFDI shall, in principle, establish the inspection sequences for pharmacological and toxicological, clinical trials, CMC development, and manufacturing sites inspections in accordance with the time sequence of the tasks received, and make overall arrangements for on-site inspection.

The inspection task received by CFDI shall be notified to the applicant through CFDI website, and the applicant may not be notified in advance for cause-related inspection.

**Article 21** If asked for Manufacturing Site Inspections, the applicant shall confirm within the prescribed time limit and submit the confirmation form to CFDI to clarify the circumstances under for this inspection; in the case of dynamic manufacturing on-site inspection, the production arrangement within the specified time limit shall also be confirmed.

Commercial-scale production process verification batches and on-site inspection dynamic production batches if needs should be organized on the planned commercial production line in accordance with the requirements of Good Manufacturing Practice of Medical Products (GMP); in principle, the batches should be consistent with the planned commercial production batches.

Section 2 Inspection plan

**Article 22** In accordance with the *Key Points and Determination Principles of Drug Registration Inspection*, based on the risk principle, and combined with the inspection objects and inspection concerns (if any) proposed by CDE, CFDI determines the inspection location and formulates an inspection plan in combination with the inspection resources, etc.

**Article 23** CFDI shall organize the implementation of the registration inspection work within the registration inspection time limit, determine the inspection time, and notify the applicant and the inspected institution to accept the registration inspection. If a dynamic manufacturing on-site inspection is required, Manufacturing Site Inspection time shall be determined based on the applicant's dynamic production arrangement.

**Article 24** The inspection team shall be composed of two or more persons who are qualified as drug inspectors, and the team leader shall assume overall responsibility. According to the specific conditions of the inspected varieties, experts in related fields may participate in the registration inspection. The CDE shall, in principle, send personnel to participate in cause-related inspections initiated by it.

The personnel participating in the registration inspection shall sign the declaration of no conflict of interest and the inspector's undertaking; if the registration inspection activities they are engaged in may cause conflicts of interest, they shall take the initiative to withdraw.

**Article 25** The drug regulatory authorities of the province, autonomous region, or municipality directly under the Central Government where the inspected institution is located shall select a drug regulatory officer as an observer to assist in the registration inspection work and be responsible for transferring the problems found in the registration inspection to the drug regulatory authorities of the province, autonomous region, or municipality directly under the Central Government.

Section 3 Implementation of on-site inspection

**Article 26** Before CFDI implements registration inspection, it shall formulate an inspection protocol in accordance with the *Key Points and Determination Principles of Drug Registration Inspection*, based on the risk principle, and in combination with the inspection objects and inspection concerns (if any) proposed by CDE. The content of the inspection protocol includes: the basic information of the inspected institution, the type of inspection, the purpose of the inspection, the basis of the inspection, the time of the on-site inspection, the content of the inspection, the members of the inspection team, etc.

**Article 27** The applicant shall coordinate with the relevant institutions of drug development, manufacturing, and registration applications and the involved manufacturers and suppliers of chemical raw materials, TCM materials, TCM decoction pieces and extracts, excipients, and packaging materials and container that directly contact drugs, or other entrusted institutions to accept on-site inspections as required, and when necessary, coordinate and organize part of the inspection-related personnel and materials to be inspected at designated locations.

The inspected institution shall cooperate with the inspection team, open relevant venues, provide documents, records, electronic data, etc. required for the inspection in a timely manner, answer the inspection team's inquiries truthfully, and ensure the authenticity of the information provided.

**Article 28** During the registration inspection work, the inspection team has the right to inspect the applicant and the inspected institution, personnel, facilities and equipment, management requirements, etc., enter the development, manufacture, and other inspection related sites, read relevant dossiers, and inquire the relevant personnel.

For the problems found in the registration inspection, the inspection team has the right to collect relevant supporting dossiers by means including but not limited to photocopying, photographing, and videotaping according to the actual situation.

**Article 29** At the beginning of the on-site inspection, the inspection team shall preside over the open meeting, present the authorization certificate to the applicant and the inspected institution, notify the inspector composition, inspection purpose and scope, declare inspection precautions and inspection disciplines, etc., and inform the rights and obligations of the inspected institution.

The inspected institution shall introduce to the inspection team the development and manufacturing of the inspected variety in the institution and clarify the person in charge of the inspection site.

**Article 30** The inspection team shall conduct on-site inspection in accordance with the requirements of the inspection protocol and the main points of the inspection, and record the inspection time, location, inspection content, and problems found in detail. When necessary, the inspection team can adjust the inspection implementation protocol based on the on-site inspection situation and the risk principle. For adjustments such as extending or shortening the inspection time, increasing, or reducing the inspection objects, etc., it needs to be reported to CFDI for approval before implementation.

**Article 31** If the inspection team needs to take samples for cause-related inspection, the inspection team shall take samples and seal them in accordance with the relevant requirements for drug sampling; the samples shall be sent to the drug testing institution for sample testing as required.

If it is deemed necessary to conduct sample inspection during the on-site inspection, the inspection team shall, with the approval of CFDI, take samples and seal them in accordance with the relevant requirements on drug sampling, and the sampling situation shall be described in the inspection report. The samples shall be sent to the drug testing institution for sample testing as required.

**Article 32** If the inspection team discovers that the applicant or the inspected institution has a situation that affects the safety of drug development and production or is suspected of violating the law, it shall immediately report to CFDI.

If the inspection team finds that the applicant or the inspected institution has a situation that affects the safety of drug development and manufacturing, it shall also inform the applicant or the inspected institution to take necessary measures to control risks in a timely manner. For suspected violations of the law, the inspection team shall record the inspection in detail, make a written record of the problems found and take various methods such as collecting or photocopying relevant documents and materials, photographing relevant facilities, equipment and materials and other physical and on-site conditions, collecting physical or electronic evidence, questioning relevant personnel and forming inquiry records according to the actual situation so as to timely fixing evidentiary materials in accordance with the requirements of relevant evidence rules.

The observer shall immediately report the relevant situation to the provincial drug regulatory authority to take corresponding measures in accordance with the law.

**Article 33** If CFDI considers that there is indeed a major risk and measures need to be taken by the NMPA after the evaluation, it shall immediately report to the NMPA and put forward handling suggestions and copy the relevant information to CDE.

Section 4 Inspection report

**Article 34** The inspection team shall discuss and summarize the on-site inspection, put forward comprehensive evaluation opinions on on-site inspection, and make on-site inspection conclusions based on the principle of inspection results, form on-site inspection reports and on-site inspection question sheets.

The on-site inspection report shall describe the on-site inspection process and results, possess basic elements such as accuracy, fairness, completeness, and logicality, and attach the required supporting proof dossiers. The on-site inspection question sheet shall include the problems or defects found in the on-site inspection.

**Article 35** Before the end of the on-site inspection, the inspection team shall preside over the close meeting, feedback the on-site inspection situation to the inspected institution and/or applicant, and report the problems found in the on-site inspection.

The inspected institution shall confirm the feedback from the inspection team, and may put forward different opinions, explanations, and explanations if there is any objection. The inspection team shall make further verification and make necessary adjustments to the relevant content of the on-site inspection report and the on-site inspection question sheet based on the inspection situation.

The on-site inspection report shall be signed by all members and observers of the inspection team.

The on-site inspection question sheet shall be signed by all members of the inspection team, observers, and the person in charge of the inspected, and shall be affixed with the official seal of the inspected institution.

If the inspected institution refuses to sign and seal, the inspection team shall indicate it in the on-site inspection report. The inspected institution shall give another written explanation on the refusal of signature and seal, which shall be signed by the person in charge of the inspected institution and stamped with the official seal of the inspected institution and submitted to the inspection team.

After the on-site inspection is completed, the inspection team shall return the supporting proof dossiers and other dossiers other than evidential dossiers to the inspected institution or delete them. The on-site inspection question sheet shall be sent to the inspected institution and the applicant.

**Article 36** The inspection team shall submit the on-site inspection report, on-site inspection question sheet and related dossiers to CFDI within the prescribed time limit as required.

The on-site inspection question sheet and related dossiers shall be submitted to the observers and sent to the relevant drug regulatory authorities of provinces, autonomous regions, and municipalities directly under the Central Government.

Section 5 Review of the inspection report

**Article 37** CFDI shall review the on-site inspection report based on the principle of determining the inspection result.

The inspection conclusion shall be made directly if the inspection conclusion can be clearly determined according to the principle of inspection result determination after comprehensive consideration of the type of varieties, nature and severity of problems discovered.

If the problems found in the on-site inspection will affect the determination of the inspection conclusion, CFDI shall request the applicant in writing to provide feedback on the relevant issues within 20 days. If the problem only needs to be explained, the applicant shall be required in writing to submit dossiers within 5 days. After reviewing the feedback and explanations, CFDI shall inspect and review conclusion. If the applicant fails to submit feedback within the time limit, CFDI shall make the inspection and review conclusion based on the existing registration inspection status.

For various types of on-site inspections that involve multiple inspection objects and sites, CFDI shall make a final inspection conclusion on the on-site inspection of all the inspection objects and sites involved.

When necessary, CFDI may organize an on-site verification.

**Article 38** For complex or controversial issues, CFDI may hold a review meeting of registration inspection experts to listen to expert opinions on inspection, evaluation, and test. CFDI shall inspect and review conclusion based on the opinions of experts.

Section 6 Disposal of inspection results

**Article 39** CFDI shall notify the applicant of the inspection and review conclusions.

**Article 40** CFDI shall send the on-site inspection report and the inspection and review conclusions and other dossiers to CDE within the prescribed time limit as required.

**Article 41** Based on the on-site inspection issues and related dossiers submitted by the observers, the drug regulatory authorities of the provinces, autonomous regions, and municipalities directly under the Central Government shall, in accordance with their daily supervision duties, review and confirm the rectification of the issues found in the on-site inspection of the inspected institution, and conduct follow-up inspections when necessary, and inform the review results to CDE in a timely manner.

**Article 42** If problems in the management system affecting the safety, rights and interests of subjects or the quality of clinical trial data are found in the on-site inspection of drug clinical trials, the drug regulatory authorities of the province, autonomous region, or municipality directly under the Central Government shall also report the review and confirmation results of the rectification situation and the handling conditions to CFDI. If the rectification is not in place and further measures need to be taken by the NMPA, CFDI may put forward handling suggestions and report to the NMPA.

**Article 43** Where the applicant, the inspected institution, and the person directly responsible are found to provide false certificates, data, materials, samples and other illegal acts that do not meet the requirements of the relevant quality management standards, the drug regulatory authorities at or above the provincial level shall deal with them in accordance with the *Drug Administration Law of the People's Republic of China* and other relevant regulations.

**Article 44** The problems of the applicant and/or the inspected institution found in the registration inspection shall serve as an important basis for CFDI to determine the registration inspection risk, determine the inspection organization mode and method, and the inspection location, as well as the basis for the division of compliance factors for the follow-up registration inspection started by CDE.

Section 7 Time limitation requirements

**Article 45** The CDE shall notify CFDI and the applicant to conduct registration inspection within 40 days after the acceptance of the drug registration application. In principle, CFDI shall complete the registration inspection and feed back to CDE 40 days before the expiration of the evaluation time limit.

In principle, the time limit for registration inspection is 120 days.

The applicant shall accept the registration inspection within 80 days from the date of receiving the inspection notification from CDE; in the case of Manufacturing Site Inspections, the applicant shall confirm Manufacturing Site Inspection items to CFDI within 20 days from the date of receipt of the relevant notification of Manufacturing Site Inspections from CDE.

**Article 46** If it is included in the priority evaluation and approval procedures, CDE shall notify CFDI and the applicant to conduct registration inspection within 25 days after the acceptance of the drug registration application. In principle, CFDI shall complete registration inspection and report back to CDE 25 days before the expiration of the evaluation time limit.

If it is included in the priority evaluation and approval procedures, the time limit for registration inspection is 80 days.

If it is included in the priority evaluation and approval procedures, the applicant shall accept the registration inspection within 60 days from the date of receiving the notification of inspection from CDE; in case of Manufacturing Site Inspection, the applicant shall confirm Manufacturing Site Inspection items to CFDI within 15 days from the date of receipt of the relevant notification of Manufacturing Site Inspections from CDE.

**Article 47** CFDI shall notify the applicant and the inspected institution 5 days before the on-site inspection; the applicant and the inspected institution may not be notified in advance for cause-related inspection.

**Article 48** The inspection team shall submit the on-site inspection report and related dossiers to CFDI within 5 days after the completion of the on-site inspection.

**Article 49** CFDI shall, within 40 days from the end of the on-site inspection, and within 20 days from the end of the on-site inspection for those included in the priority evaluation and approval procedures, complete the review of the inspection report, make the review conclusion, and report the registration inspection and inspection results to CDE.

**Article 50** Samples taken during inspection shall be delivered to the designated drug testing institutions within 10 days from the date of sampling.

**Article 51** The necessary feedback or explanation submitted by the applicant after the on-site inspection, the delay of the on-site inspection by the applicant due to force majeure, and the convening of the expert consultation meeting shall not be included in the time limit. Where relevant circumstances affect the time limit for registration inspection, CFDI shall notify CDE.

**Article 52** If it is necessary to extend the time limit due to the variety characteristics or special circumstances of registration inspection, the applicant shall be informed in writing of the extension of the time limit, and CDE shall be notified, or other relevant professional and technical institutions shall be notified when necessary. The extension time limit shall not exceed one half of the original time limit.

Section 8 Handling of special circumstances

**Article 53** After CDE notifies the applicant of registration inspection within the prescribed time limit, in principle, CFDI shall terminate the relevant registration inspection task, explain the reasons and basis, and inform the CED in case of the following circumstances.

(I) The applicant fails to carry out Manufacturing Site Inspection within the prescribed time limit, or fails to accept on-site inspection within the prescribed time limit, except for the legitimate reasons of force majeure such as natural disaster or government acts;

(II) The applicant and the manufacturer have not obtained the corresponding drug production license, or the product has not completed the process verification of commercial large-scale manufacturing;

(III) The CDE notifies the termination of the registration procedure or rejects the registration for the variety whose registration inspection has not been completed;

(IV) Other conditions require the termination of registration inspection.

**Article 54** If the applicant and/or the inspected institution refuses, obstructs, restricts the inspection, fails to cooperate in providing necessary supporting materials, etc., or have subjective intention to make the inspection fail, the inspection result is directly judged as not passed.

**Article 55** If the applicant or the inspected institution believes that there is a conflict of interest between the inspector and the inspection item they are engaged in, it may submit a withdrawal request with related reasons to CFDI before the end of the open meeting of the on-site inspection. If CFDI confirms that it is a situation that requires withdrawal, the relevant personnel shall be withdrawn.

If the applicant or the inspected institution has different opinions on the on-site inspection procedures, the problems found in the inspection, etc., they may raise an objection to CFDI within 5 days from the end of the inspection.

CFDI shall investigate or study the objections raised and inspect and review conclusion based on the investigation and study.

**Chapter IV Supplementary Provisions**

**Article 56** Regarding the registration inspection of overseas sites, CFDI shall organize the implementation in accordance with the *Provisions on the Administration of Overseas Inspection of Drugs and Medical Devices* and other relevant requirements.

**Article 57** The sampling referred to in the Procedures refers to the sampling, sample sealing and notified inspection conducted by the drug regulatory authority during the registration inspection process.

**Article 58** The time limit mentioned in the Procedures is calculated based on working days.

**Article 59** CFDI is responsible for the interpretation of the Procedures.

**Article 60** The Procedures shall come into force as of January 1, 2022.