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Problems and Countermeasures of Quality Control of Drug Non-Clinical Trial Items

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Abstract: Non-clinical trial of drugs is a key link in drug research and development, and its quality control directly affects the safety and effectiveness evaluation of drugs. At present, non-clinical drug trials are faced with many quality control problems, such as imperfect design of trial scheme, nonstandard operation of personnel, improper management of instruments and equipment, chaotic data recording and management, and ineffective implementation of quality assurance system, which may lead to deviation of test results and even failure of drug research and development. In this paper, the main problems existing in the quality control of drug non-clinical trial items are deeply analyzed, and the corresponding improvement countermeasures are put forward from the aspects of optimizing the design of test scheme, standardizing the test operation process, improving data management and recording, strengthening the quality assurance system and strengthening external cooperation and communication. Through these measures, we can effectively improve the quality control level of drug non-clinical trials, ensure the scientificity, accuracy and repeatability of test results, lay a solid foundation for drug research and development, and promote the healthy development of pharmaceutical industry.

1. Introduction

In the long journey of drug research and development, the non-clinical trial stage plays a crucial role. It not only provides data support and theoretical basis for subsequent clinical trials, but also is an important pre-link to determine whether drugs can be successfully marketed and safely and effectively applied to the treatment of human diseases. In recent years, with the rapid development of medical science and technology and the continuous improvement of public requirements for drug quality and safety, drug non-clinical trial projects are facing unprecedented opportunities and challenges.

On the one hand, new science and technology, such as gene editing, organ-like cultivation and high-resolution imaging technology, are constantly emerging and applied in the field of drug research, which enables us to explore the mechanism of action, pharmacodynamics and toxicological characteristics of drugs from a more microscopic and accurate perspective. These technological innovations have brought higher efficiency and resolution to drug non-clinical trials, which is expected to accelerate the process of drug research and development and improve the quality of drugs [1]. However, on the other hand, with the improvement of technical complexity and

the expansion of research scope, the difficulty of quality control of drug non-clinical trial projects has also increased exponentially. This spans from the standardized care of experimental animals to the scientific rigor and soundness of complex experimental designs. From the accurate calibration and maintenance of various instruments and equipment to the accurate collection, recording and analysis of experimental data, there are hidden quality risk points that may affect the authenticity, reliability and repeatability of experimental results.

At present, there are many cases of drug research and development failures caused by the quality problems of non-clinical trials in the global pharmaceutical industry, which not only causes a huge waste of research and development resources, but also delays the listing process of many new drugs that need to be treated urgently, which has an indirect negative impact on the health and well-being of patients [2]. Under this background, it has become an urgent task for the whole pharmaceutical industry to deeply analyze the existing problems in quality control of drug non-clinical trial projects, such as the loopholes in quality management system, the lack of professional quality and training of personnel, and the deviation in the implementation of standard operating procedures (SOP), and to explore practical countermeasures. By strengthening the quality control system to ensure the accuracy and integrity of drug non-clinical trial data, we can lay a solid foundation for drug research and development, promote the steady development of the pharmaceutical industry in a safer, more efficient, and more innovative direction, and ultimately benefit the majority of patients and meet their growing medical and health needs.

2. Present situation and regulatory requirements

Table 1 Comparison of global GLP regulatory requirements for non-clinical trials of drugs

Region/institution	Regulatory framework	Core requirements	Scope of implementation	Regulator
China (NMPA)	Quality Management Standard for Non-clinical Research of Drugs	Laboratory facilities verification, SOP filing, data life cycle management [4]	All registered non-clinical studies	National Medical Products Administration
United States (FDA)	21 CFR Part 58 (GLP)	Independent quality assurance department, original data preservation ≥2 years, and animal welfare compliance review [5]	Study on the Safety of Drugs and Medical Devices	FDA Inspector's Office
EU	OECD GLP/EMA guide	Multilingual SOP support, environmental monitoring reports, and cross-border data mutual recognition [6]	Safety assessment of chemicals and biological products	GLP supervisory bodies of member countries
ICH	ICH S series guide	Research and design standardization, risk analysis and integration, and electronic data system verification (ALCOA+ principle) [7]	International multi-center research coordination	Regulators of member States

At present, the quality control of drug non-clinical trials faces multiple challenges. Due to resource constraints, it is difficult for academic medical institutions and small and medium-sized research institutions to establish a complete GLP compliance system, resulting in insufficient infrastructure and compliance processes. Data integrity is the core concern, especially in electronic record management, audit trail and process transparency, and about 30% of FDA warning letters are related to this [3]. In addition, researchers do not fully understand GLP regulations, especially lack

of professional training in emerging fields such as cell and gene therapy, which increases the risk of operational deviation. Multi-center research needs to unify equipment calibration, data acquisition and reporting standards to improve data consistency. In low-income countries, backward technical facilities and shortage of regional experts make it take more than 24 months to complete GLP certification on average, which shows great challenges in technology and certification.

There are differences in the requirements of GLP from major global regulators, but the core goal is to ensure the traceability and repeatability of the research, as shown in Table 1.

At present, the key issues of quality control of drug non-clinical trials focus on data governance, compliance resource allocation and regulatory synergy. Promoting the application of electronic systems, such as platforms conforming to the 21 CFR Part 11 standard, will help to improve data integrity and reduce human errors, but the cost and adaptability of small and medium-sized institutions should be taken into account. In the case of limited resources, it is suggested to adopt a step-by-step certification strategy, give priority to GLP certification of key modules, and then gradually cover the whole process. At the same time, promoting the process connection between GLP and GMP and GCP through ICH and other international organizations can enhance regulatory synergy, reduce repeated review and improve the overall research efficiency.

3. Main problem

3.1. Problems in the design of test scheme

(1) The scheme is not perfect or targeted.

Some experimental schemes may not fully consider the characteristics, mechanism of action and expected use of drugs when designing, resulting in unclear experimental purposes. For example, for some drugs with special pharmacokinetic characteristics, the corresponding sampling time and detection index are not clearly defined in the scheme, which makes it impossible to accurately evaluate the absorption, distribution, metabolism and excretion of drugs in vivo.

The potential toxic target organs and types of toxic reactions may not be fully considered in the test scheme, which leads to the failure to find the possible toxic reactions of drugs in time during the test. Some drugs may be mainly toxic to the nervous system, but there are no targeted neurobehavioral detection indicators in the experimental scheme, thus missing important toxicity information.

(2) The setting of control group is unreasonable

The control group is the key reference to evaluate the drug effect, but in some experiments, there may be problems in the setting of the control group. There is no suitable blank control group, which makes it impossible to accurately judge the role of the test drug itself; Or there is no solvent control group, so it is difficult to distinguish between drug effect and solvent effect. In addition, the selection of positive control group may be inappropriate, such as the dose and route of administration of positive control drugs do not match with the experimental drugs, which leads to the decrease of comparability of test results.

(3) Sample size estimation is inaccurate

The sample size directly affects the statistical significance and reliability of the test results. If the sample size is too small, it may lead to an increase in the contingency of the test results and cannot accurately reflect the real effect of the drug; However, if the sample size is too large, it will increase the test cost and waste resources. In the design of actual experimental scheme, the sample size estimation may be unreasonable due to inaccurate expected estimation of drug effects or insufficient understanding of statistical methods.

3.2. Operational problems in the test process

(1) Personnel operation is not standardized

Non-clinical trials of drugs involve many operations, including animal feeding management, drug preparation and administration, sample collection and processing, etc. In these links, the nonstandard operation of personnel may lead to the deviation of test results. For example, in the process of raising animals, feeding, cleaning and observation of animals are not carried out in strict accordance with the operating procedures, which may affect the health status of animals and the stability of test results; In the process of drug preparation, the drug is not accurately weighed or dissolved according to the prescribed method, which may lead to inaccurate drug concentration and further affect the test results. The operation differences between different operators may also have an impact on the test results. If there is no unified operation standard and training, different personnel may have differences in techniques, strength and time during operation, which will lead to the reduction of repeatability and reproducibility of test data.

(2) Improper use and maintenance of instruments and equipment

The accuracy of instruments and equipment used in the test process directly affects the quality of test data. If instruments and equipment are not calibrated and maintained regularly, measurement errors may occur. If the high performance liquid chromatograph (HPLC) used to detect drug concentration is not verified and calibrated regularly, the results of drug concentration determination may be inaccurate. If the instrument used to record animal physiological parameters fails or is not maintained in time, the data record may be incomplete or inaccurate. The use environment of instruments and equipment may also have an impact on the test results. Environmental factors such as temperature and humidity do not meet the use requirements of instruments and equipment, which may affect the performance of instruments and the accuracy of measurement results.

(3) Sample management confusion

The collection, storage and transportation of samples are the key links in the test process. Improper sample management may lead to sample degradation, pollution or loss, thus affecting the test results. For example, in the process of sample collection, samples are not collected according to the prescribed time and method, which may lead to changes in drug concentration or biomarkers in the samples; In the process of sample preservation, failing to preserve the sample according to the required temperature and conditions may lead to the degradation or denaturation of the components in the sample; In the process of sample transportation, failure to take appropriate protective measures may lead to damage or pollution of samples during transportation.

3.3. Problems in data management and recording

There are many problems in data management and recording, which affect the accuracy and reliability of test results. Incomplete or inaccurate data records often occur, such as failure to record experimental animal information or drug administration parameters in detail, which may lead to analysis deviation and poor repeatability of results. Inconsistent or nonstandard recording formats also increase the difficulty of data processing and increase the error probability. In the process of data processing and analysis, improper operations, such as incorrect data cleaning or inappropriate statistical methods, may lead to the distortion of conclusions, and the subjective bias of analysts may also affect the objectivity of interpretation of results.

3.4. The problem of poor implementation of quality assurance system

The imperfection of quality assurance system directly affects the overall quality control of drug

non-clinical trials. Many institutions lack a systematic review mechanism of experimental schemes and an effective personnel training system, which makes it difficult to find and correct problems in time. At the same time, irregular document management also hinders the accurate implementation of operating standards, which in turn leads to quality control loopholes and affects the scientificity and reliability of the test.

There are some problems in quality supervision and inspection, such as the lack of regular on-site inspection and data audit, which lead to irregular operation, improper use of equipment or data recording errors. More importantly, the feedback and rectification mechanism after problems are found is not perfect, which makes similar problems appear repeatedly and hinders the continuous improvement of the quality management system.

4. Improvement countermeasures

The quality control of drug non-clinical trials is an important guarantee to ensure the quality and safety of drug research and development. By optimizing the design of test scheme, standardizing the test operation process, perfecting data management and recording, strengthening the quality assurance system and strengthening external cooperation and communication, the problems existing in the quality control of non-clinical drug trials can be effectively solved, and the scientific, accurate and repeatable test results can be improved.

4.1. Optimize the design of test scheme

To optimize the design of experimental scheme, we should start from three aspects: clear research purpose, reasonable setting of control group and scientific estimation of sample size. Under the multi-disciplinary cooperation, combined with drug characteristics, mechanism of action and potential risks, we should formulate targeted and comprehensive experimental objectives, and design matching experimental models and detection indicators. At the same time, by setting up blank, solvent and positive control groups, the comparability and reliability of the results are improved. Finally, scientifically calculate the sample size based on statistical principles to ensure that the experiment has sufficient efficacy, which not only meets the research needs but also avoids the waste of resources.

4.2. Standardize the test operation process

(1) Strengthen personnel training and management

The relevant departments should establish a perfect personnel training system and conduct systematic theoretical and practical training for testers. The training content should encompass the design of test schemes, animal feeding management, drug preparation and administration, sample collection and processing, instrument and equipment operation, and other essential areas to ensure that testers are familiar with and proficient in every aspect of test operations. Regular assessments of testers should be conducted to evaluate their operational skills and quality awareness. Testers who fail the examination should be suspended from participating in experiments until they undergo retraining and pass the examination. At the same time, relevant departments should establish an incentive mechanism to encourage testers to actively participate in training and quality improvement activities.

(2) Standardize the management of instruments and equipment

Relevant departments should establish an instrument and equipment file management system, and refine the procedures of procurement, acceptance, installation, debugging, calibration, maintenance and repair. Relevant departments need to calibrate and verify the performance of

instruments and equipment regularly to ensure that they are kept in the best working condition. Formulate operating procedures for instruments and equipment, and define operating steps, precautions and maintenance requirements. When using instruments and equipment, strictly abide by the operating rules to prevent instrument failure or measurement error caused by improper operation.

(3) Strengthen sample management

The relevant departments should standardize the standard operating procedures (SOP) for sample management, detailing the specific requirements for collection, storage, transportation, and processing. It is necessary to ensure that the relevant personnel strictly abide by the prescribed time and method in the sampling process to maintain the integrity and stability of the sample, implement a powerful sample identification and traceability system, assign a unique identifier to each sample, and carefully record its source, collection time, processing history and test results for seamless verification and audit trail when necessary.

4.3. Improve data management and recording

Relevant departments should develop a standardized data recording format and specification, requiring testers to record data accurately, completely, clearly and timely. Data records should include detailed information about experimental animals, drug preparation and administration, sample collection and testing, and any abnormalities observed during testing. Relevant departments need to establish an audit mechanism for data records, which will be regularly audited by specialized personnel to ensure the integrity and accuracy of data. For the problems found, they should be fed back to the tester in time and asked to correct and supplement them.

Professional data processing software and statistical analysis methods are adopted to scientifically process and analyze the test data. In the process of data processing, we should follow the principle of data cleaning, remove obvious abnormal values and erroneous data, but at the same time ensure the authenticity and integrity of the data. In the process of data analysis, relevant personnel should avoid the influence of subjective prejudice and strictly follow statistical principles and methods. For complex data analysis problems, statistical experts are invited for guidance and consultation to ensure the scientific and reliable analysis results. Relevant departments need to establish a data security management system, implement effective data encryption and access control measures to prevent data leakage, tampering or loss. Back up data regularly to ensure timely recovery in case of accidents.

4.4. Strengthen the quality assurance system

(1) Improve the quality assurance system architecture

Relevant departments should establish a sound quality assurance system covering all aspects, including test scheme design, test operation, data management, personnel training and instrument and equipment management. Relevant departments need to clearly define the responsibilities and authority of the quality assurance department to ensure its ability to independently and objectively supervise and manage the whole testing process, develop a comprehensive quality assurance document system, including quality manuals, program documents, operating procedures and record forms. These quality assurance documents should specify all quality control requirements and operational procedures to ensure that testers have clear guidelines to follow during the operation process.

(2) Strengthen quality supervision and inspection

The relevant departments should establish a regular quality supervision and inspection mechanism to conduct on-site inspection and data audit of the testing process. The inspection

contents should include the implementation of the test plan, the standardization of the test operation, the completeness and accuracy of data records, the use and maintenance of instruments and equipment, etc. The problems found in the inspection shall be promptly fed back to the relevant responsible person and required to be rectified within a time limit. After the rectification is completed, it should be rechecked to ensure that the problem is completely solved. At the same time, the relevant departments should establish a quality inspection report system to record the inspection results and rectification as the basis for quality evaluation and continuous improvement.

(3) Promote continuous quality improvement

The relevant departments should establish a quality evaluation index system to evaluate the testing quality regularly. Evaluation indicators should include the accuracy, repeatability, and reproducibility of test results, the integrity of data records, the standardization of test operations, and the coverage of personnel training. Based on the quality evaluation results, develop a quality improvement plan, clearly defining improvement goals and measures. Through continuous quality improvement activities, the quality level of drug non-clinical trials will be continuously improved to ensure the scientificity and reliability of test results.

4.5. Strengthen external cooperation and exchanges

(1) Maintain close communication with regulatory agencies

Drug non-clinical trial institutions should keep close contact with drug regulatory agencies, and timely understand and master the latest regulatory requirements and technical guidelines. During the test, relevant personnel actively accept the supervision and guidance of the regulatory authorities to ensure that the test complies with relevant laws and standards. Any major problems or uncertainties that arise during the test should be promptly reported to the regulatory authorities, and their opinions and suggestions should be sought. At the same time, relevant personnel should actively participate in training courses and seminars organized by regulatory agencies to enhance their understanding and implementation of laws and regulations.

(2) Carry out industry exchanges and cooperation

Testers should strengthen communication and cooperation with peer institutions and share experimental experience and quality control methods. By participating in industry conferences, academic seminars, and technical exchange activities, we can gain insights into the latest progress and quality control trends of non-clinical drug trials both domestically and internationally, and learn advanced management experiences and operational technologies. Relevant departments should establish an industry quality control alliance to jointly formulate and popularize unified quality control standards and operating procedures. Through mutual inspection and evaluation within the alliance, the quality control level of various institutions will be promoted and the healthy development of the whole industry will be promoted.

5. Conclusion

The quality control of drug non-clinical trial projects faces many challenges, such as data governance, compliance resource allocation and regulatory coordination, which are manifested in imperfect trial design, improper personnel operation and instrument maintenance, chaotic sample management and inaccurate data records. In order to solve these problems, a series of improvement measures need to be taken: relevant personnel need to optimize the design of test scheme to enhance its scientific rigor and reliability; Relevant departments need to strengthen personnel training and equipment management to ensure compliance with operating norms and keep equipment in the best condition; Strengthen sample management, unify data recording format, and ensure the accuracy and integrity of data; Improve the quality assurance system structure, strengthen quality supervision

and inspection, and promote continuous improvement; Improve the overall quality control level through continuous communication with regulatory agencies and active participation in industry exchanges. These improvement measures can effectively improve the scientificity, accuracy and repeatability of the test results, provide a solid guarantee for drug research and development, and promote the development of the pharmaceutical industry.

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