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Comparative Analysis of Domestic and International Drugs Microbiological Testing Methods

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Abstract: Under the background of the new era, The United State puts forward higher requirements for the pharmaceutical industry. As one of the important indexes to evaluate the safety of drugs, the microbiological test of drugs is used to detect whether a drug is contaminated by microorganisms during the development, production and storage of the drug. The accuracy of test and measurement results is not only affected by the laboratory quality control and the expertise of the testing personnel, but also by the testing technology. Based on the comparative analysis of domestic and international drug microbiological testing methods, this study believes that in the past decades, Chinese drug microbiological testing technology has made certain breakthroughs, but compared with other developed countries, Chinese microbiological testing technology is at the initial stage, there are problems such as immature technology. In addition, Chinese microbiological testing laboratories are short of funds, relatively backward testing hardware and facilities, lack of professional testing talents, and many operations are not carried out as required. This study has certain theoretical and practical significance, which enriches the content of Chinese drug microbiological testing technology, and plays a guiding role in the innovation of Chinese drug microbiological testing method in practice.

1. Introduction

In the way to improve the drug quality, drug microbiological inspection is one of the important means. Only strengthen the importance of drug microbiological inspection can guarantee and promote the efficacy of drugs after being put into the market [1]. Due to the different characteristics of drugs, there are many kinds of microbes in them, and many drugs cannot resist the existence of microbes [2]. At present, there are more and more methods of drug microbiological inspection and detection, and their application scope has been gradually expanded [3]. In the work of drug microbiological inspection, inspectors, equipment, environment and other factors can influence the accuracy of test results. Only strict control of these factors can ensure the quality of drug microbiological inspection [4].

Dug microbiological inspection is one of the important means to evaluate the quality and safety of drugs. It evaluates the safety of drugs through the application of microbial technology to detect whether drugs are contaminated by microorganisms in the process of r&d, production and storage

[5]. However, in recent years, tragedies caused by microbial contamination of drugs have occurred repeatedly, leading to a major test of the ability of microbial testing of drugs, and the accuracy, scientific nature and timeliness of test results have laid a foundation for the safety and reliability of drugs [6]. In pharmaceutical microbial quality control and testing, an important prerequisite is to ensure that have corresponding hardware and software, which not only have the hardware quality assurance as the foundation, also has advanced inspection technology, complement the success can ensure the accuracy of testing, and thus draws the scientific test results [7].

It was reported that in July 1970 and the following months, 40 patients died of sepsis due to the infusion of bacteria-contaminated glucose in 25 hospitals in the United States [8]. In China, there are also cases of death caused by microbial contamination of drugs. From 1991 to 1993, there were 46 cases of infection and 8 deaths in a hospital infusion [9]. Therefore, due to the importance of microbial detection, we should pay attention to how to strengthen and innovate the ability of microbial detection of drugs [10]. The purpose of this paper is to compare and analyze the microbiological testing technology of drugs in microbiological laboratories at home and abroad, so as to get some experience and make prediction and prospect for the development trend of microbiological testing technology of drugs.

2. Theoretical Basis

2.1. Characteristics of Microbial Detection of Drugs

To put it simply, microbiological test of drugs is to control the quality of microorganisms in drugs. It covers a wide range of tests, including the production environment, culture conditions and sampling test of drugs. When testing drug microorganisms, it is not only necessary to have advanced hardware infrastructure and scientific testing technology, but also to pay attention to factors such as the laboratory environment and the normal operation of key equipment in sampling testing. In addition, the microbiological testing of drugs has certain requirements on the laboratory system, such as the safety, reliability and scientific nature of the test. In particular, test operators must pay attention to their own safety and operate in strict accordance with the rules and regulations to ensure the clean and safe experimental environment. In addition, biosafety cabinets are indispensable for microbial testing of drugs. By replacing cultures and other infectious materials, the life safety of operators can be guaranteed. In addition, as toxic substances or bacterial infections are easy to occur in the process of experiments, biosafety cabinets can effectively reduce the occurrence of cross-infections.

2.2. Significance of Microbiological Testing of Drugs

Generally speaking, safety is a priority in the use of drugs. When the preparation is contaminated by microorganisms, even if the degree is very small, it will seriously threaten the safety of patients. Therefore, sterility test must be carried out according to the regulations to ensure the safety, scientific and effectiveness of the medication. At present, the scope, content, method and sampling of sterility test are clearly stipulated in almost all countries' pharmacopoeia, and even incorporated into the national legal system. The Chinese Pharmacopoeia also has detailed provisions on drug microbiological testing, so we must attach great importance to drug microbiological testing to prevent the disease before it occurs. Once the drugs are invaded by exotic bacteria, the acidity and alkalinity of the drugs will change. In some cases, the drugs will become ineffective. In some cases, the toxins similar to Pseudomonas aeruginosa may be produced, which may lead to ulcers, blindness and other symptoms. The harmful effects of bacteria are very great, so the survival rate of bacteria can be effectively controlled and the quality and safety of drugs can be guaranteed by

establishing corresponding microbial detection standards.

3. Microbial Detection Technology

To encourage innovation in the pharmaceutical industry, the US Food and Drug Administration (FDA) launched the Process Analysis Technology (PAT) Program in 2002, which aims to encourage pharmaceutical companies to apply a variety of modern technologies to achieve real-time and accurate judgment and control of pharmaceutical processes. Drug microbiological inspection is mainly divided into two parts: production process monitoring and delivery inspection. The production process monitoring includes the inspection of raw and auxiliary materials and intermediate products, the monitoring of pharmaceutical water, the identification and analysis of microbial drug fermentation strains, and the monitoring, investigation and tracing of environmental microorganisms; Factory inspection includes sterility test of final products, microbial limit test of non-sterile products, identification and analysis of microbial strains, etc. The relevant methods of microbial detection and analysis of drugs cover the detection, screening, counting and identification of microorganisms. Traditional microbial detection method is simple and effective and relatively low cost and is suitable for most of the microbiological testing laboratory, but there is also a test cycle is long, can not be real-time feedback situation, hindered the microbial production process in real-time monitoring, still need to improve the innovation to adapt to the modern pharmaceutical industry based on process control and risk assessment management mode.

4. Comparative Analysis of Domestic and Foreign Microbiological Testing Methods

4.1. Comparison of the Development History and Status Quo of Domestic and Foreign Drug Microbial Detection Methods

Globally speaking, the leading microbial detection technologies for drugs include: testing technologies based on microbial growth information, such as bioluminescence technology, electrochemical technology, turbidimetry, etc. Testing techniques for the direct determination of living microorganisms in the measured media, such as solid phase cell counting, flow cytometry, etc.; Analysis techniques based on specific components of microbial cells, such as fatty acid determination, nucleic acid amplification, gene fingerprint analysis, etc. The isolator technology has long been certified by the FDA and the European Commission for The Regulation of Medicines because it not only reduces the impact on the operator, but also reduces the risk of microbial contamination of the drug. However, the isolator technology is not widely used in China. In the future, it is one of the requirements of the development trend of the laboratory environment with high cleanliness. The following is to select common domestic and foreign drug microbiological detection technology for detailed comparative analysis.

4.2. Comparison of Existing Detection Techniques for Pharmaceutical Microorganisms at Home and Abroad

At present, there are many methods for the determination of drug microorganisms at home and abroad, and the most common method is culture and separation. However, its cumbersome testing procedure not only occupies a large amount of resources, but also has a long testing period, which is not conducive to the online control and rapid response of microbial detection exceeding the standard. Therefore, the innovative rapid microbial detection method has been paid more and more attention by scholars and scientists all over the world, and the search for scientific and rapid microbial detection methods for drugs has also become a research hot spot. In recent years, new

technologies and methods have been widely used in the field of drug microbiological inspection, which has greatly improved the detection efficiency and speed. The current rapid microbial detection methods combine the knowledge of microbiology, molecular chemistry, biochemistry, biophysics, immunology and serology to separate, detect, identify and count microorganisms, which is faster, more convenient and more sensitive than the traditional methods. At present, common rapid microbial detection methods include: ATP-based microbial detection, immunology technology, PCR technology, gene chip technology, biosensor technology, biological particle counter technology, etc. Some of these methods have been mature and have been widely used in the field of drug microbial detection. Table 1 summarizes and compares the current microbial classification methods of drugs in order to analyze the characteristics of various microbial detection techniques.

Table 1 Summary of the comparison of various microbial detection techniques at home and abroad

Detection method	Applicable condition	Detect target	Limitations
Traditional culture method	Culturable microorganisms,	By colony characteristics	Length of detection cycle and limited range of cultivation
AIP test	The total amount of living microorganisms	ATP fluorescence intensity	Only the total amount of live microorganisms can be detected
Rabbit epidemiology	Mainly used to classify the serotypes of different strains within the species	Antigen antibody reaction	It is necessary to increase bacteria first; Operation is complicated; Difficult to be automated
The PCR	A microbe known to contain nucleic acid	Fluorescence intensity of dyes on DIA	Only microorganisms with known sequences can be detected
Gene chip technology	Microbe gene sequencing requires a large sample size	Gene sequencing	PCR amplification is required before hybridization detection can be performed
Gene probe technique	Genomics studies used to label genes whose partial sequences are known	Gene sequence study	Gene sequences should be understood before PCR amplification
Biosensor|	Biometric response	Change in response	Poor universality; specific design for the target; technology is not mature enough
Biological particle count	Number of living microbe particles	Fluorescence of tryptophan on air particles	Only the total amount of biological particles can be detected

4.3 Development of Drug Detection Technology at Home and Abroad

In China and other countries, there are also great differences in the limitation standards of drug microbial detection technology. As shown in Figure 1 and Table 2, the microbial restriction varieties in the pharmacopoeia of the four countries are constantly expanding. At the same time, each country's requirements for viable bacteria also have their own characteristics. Although the drug microbiological testing in China started relatively late, based on the advanced microbiological testing technology of western developed countries and combined with the actual national conditions of China, China needs to further improve the software and hardware equipment of drug microbiological testing. At the same time, the detection technology of pharmaceutical

microorganisms in China is developing towards standardization and scientization, and there are standard rules and regulations in the aspects of inspection items, inspection methods and the basis of the formulation of pharmacopoeia, etc., especially in the research of sterile preparations, China has made some achievements. However, there is still a shortage of relevant professional experimental operators in China. Therefore, the government and universities should strengthen cooperation to increase the number of talents in this field. As a kind of drug technology evaluation, drug microbiological testing technology is a comprehensive multi-specialty science with a considerable technical content, which poses great challenges to the testers. It is obviously not advisable to conduct the testing in a closed-door manner. Keeping an open mind is the premise of adapting to the development and the internal requirement of the law of drug microbial detection technology.

Table 2 The viable bacteria of the four countries standard request.

Number of living bacterium(1ml)	Need air bacteria	Fungi
CP	10^2-3×10^4	0-10^2
BP	10^2-10^7	10^2-10^5
JP	10^2-10^3	5×10-5×10^2
USP	10-10^4	10-10^3

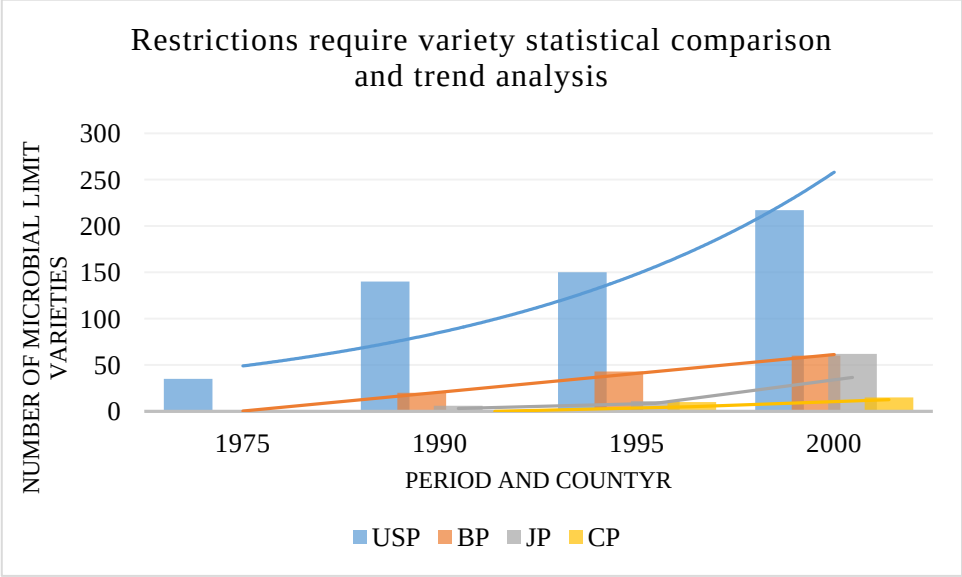

Figure. 1 Restrictions require variety statistical comparison and trend analysis

5. Summary

With the rapid development of Chinese economy and society and the continuous development of the medical level, the government has increasingly higher requirements for the quality and safety of drug production, so the requirements for drug inspection technology are also constantly improving. From the above comparative analysis, it can be seen that although Chinese microbiological testing technology does not have the long-term development foundation of foreign countries and there are still some defects in the technical aspects, under the requirements of the development of Chinese drug industry and the standardization of drug testing, Chinese drug microbiological testing

technology is constantly improving. It is worth noting that, due to the problems of backward management mode and low overall quality level of personnel, the innovation of pharmaceutical microbiological inspection technology in China needs to be further improved.

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