Development Investigation of Biomedical Reference Material in Promoting National Health

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Keywords: Traceability, Biomedical Metrology, Invitro Diagnostic Reagents.

Abstract: Biomedical reference material is a kind of important tool used in biopharmaceutical companies and health service centres to ensure the accuracy and reliability of measurement instrument. It can be traced to the source of quantity value through an uninterrupted traceability chain. Firstly, based on the detailed discussion of the development status of reference materials, it is focused on the classification and characteristics in this paper. Secondly, the management methods and application status in COVID-19 have been detailed. Finally, it explores the application research invitro diagnostic reagents and the key contents of biomedical metrology in national health service.

1 INTRODUCTION

Metrology is the key for human beings to explore the world, and measurement is the basis for realizing the unity of units and ensuring the accuracy of quantities. With the continuous pursuit of the reliability and comparability of results, reference materials, as an important tool for measuring instrument calibration and measurement method evaluation and confirmation, are being more and more widely used. The proposal of "Precision Medicine" and "National Health" promotes the importance of metrology field on the accuracy and reliability of clinical medicine, chemical analysis and biological analysis measuring instruments.

As the main carrier to ensure some medical instruments' reliability used by medical institutions, biopharmaceutical companies and health service centers, biomedical reference materials are always in the core and key position. By the uninterrupted traceability chain, they can be traced to the source of value source for maintaining the consistency and accuracy of global measured value.

2 REFERENCE MATERIALS

At present, measurement technology institutions at home and abroad have a wide variety of types and are distributed in different countries, among which the American Institute of standards and Technology, the German Federal Institute of physics and Technology and the British Government Chemist Laboratory have developed most rapidly. They have invested a lot of human, material and financial resources, and become a technical leader integrating measurement standards and laboratory capability verification.

According to foreign research hotspots, investigation direction of reference materials is different, as summarized below:

(1) United States: inorganic solution, organic solution, acidity and materials, dyes, sediments, minerals, soil and particles;

(2) Germany: water, acidity, conductivity, metals and metal alloys, advanced materials;

(3) Japan: advanced materials, food, sediments, minerals, soil and particles;

(4) Other countries: research has been carried out in advanced materials, gases, food, films and engineering nano materials.

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Fan, P., Zhao, H., Zhao, Y., Liang, L. and Chen, S.
Development Investigation of Biomedical Reference Material in Promoting National Health.
DOI: 10.5220/0011374900003443
In *Proceedings of the 4th International Conference on Biomedical Engineering and Bioinformatics (ICBEB 2022)*, pages 973-978
ISBN: 978-989-758-595-1

The development of reference materials in China also started earlier, paying great attention to the preparation of reference materials, and carrying out legal management on the approval and production. We have invested a lot of funds for long time. After about ten years of efforts, fruitful results have been achieved, and the types of national reference materials have increased year by year.

According to uncertainty range of reference materials, China classifies them into two categories: national primary reference materials (GBW XX....) and national secondary reference materials (GBW(E) XX....). According to different characteristic values, reference materials are usually divided into 13 categories, which are numbered by large category number, small category number and approval time sequence. As shown in the Tab.1 below, the category of reference materials can be identified according to numbering rules.

Table 1: Classification table of reference materials.

Category	Numbering Rules	Category	Numbering Rules
steel composition	GBW01~ GBW(E)01~	environmental chemistry	GBW08~ GBW(E)08~
gas composition and metals	GBW02~ GBW(E)02~	biomedical and drugs	GBW09~ GBW(E)09~
building material	GBW03~ GBW(E)03~	food ingredients	GBW10~ GBW(E)10~
composition analysis and radioactivity of nuclear materials	GBW04~ GBW(E)04~	composition analysis and physical properties of coal and petroleum	GBW11~ GBW(E)11~
properties of polymer materials	GBW05~ GBW(E)05~	engineering technical characteristics	GBW12~ GBW(E)12~
chemical product composition	GBW06~ GBW(E)06~	physicochemical properties	GBW13~ GBW(E)13~
geological and mineral composition	GBW07~ GBW(E)07~		

3 BIOMEDICAL REFERENCE MATERIALS

3.1 Development Analysis

Internationally, developed countries such as Europe, America and Japan have taken the lead in technology. Their biomedical reference materials have many types and high quality. They have covered all measurement fields, including small molecules, macromolecules, inorganic, organic, pure products and matrix, and most of them have been used in clinical practice. For example, reference materials in the European Union are the main ones, and the development of reference materials in metabolites, non-peptide-hormones, electrolytes, enzymes, drugs, etc. is relatively complete; Singapore, France and other countries are also catching up. They have developed corresponding reference materials lists in terms of metabolites and conducted strict interchangeability research, which could provide more interchangeability information.

At home, the technology of reference materials has been very mature, especially the reference materials for small molecular metabolites are relatively complete, but there are still many fields that are very scarce or even blank. They are mainly developed by National Institute of Metrology (NIM), the first hospital of Peking University, Beijing Institute of medical device inspection, etc. And some projects have been used to improve clinical practice. In the research of certified clinical reference materials, NIM and the clinical laboratory center of the Ministry of health have developed metabolites and non-peptide hormone reference materials by using isotope dilution mass spectrometry; Taking Beijing Aerospace general hospital and Beijing Chaoyang Hospital as representatives, some metabolites and electrolyte reference materials were developed by using other principles, which played a role in the quality control for clinical laboratories; The clinical enzymology reference material was developed by using the network fixed value of enzymology reference laboratory established in China.

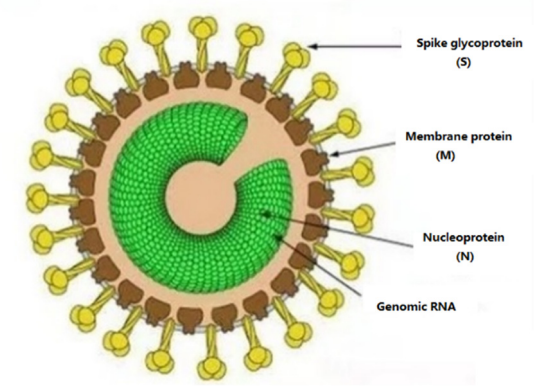

Figure 1: COVID-19.

Since the outbreak of COVID-19, biological nucleic acid reference materials have developed rapidly, and various life invitro diagnostic reagents have emerged one after another. How to quickly extract virus DNA by pharyngeal swab method, realize rapid virus detection and develop biological vaccine has become a common problem all over the world. Nucleic acid detection is an effective method to detect pathogenic microorganisms in clinic. In particular, the detection of COVID-19 and bacterial 16SrNA genes has been considered the gold standard for detection by real-time fluorescence quantitative PCR. China's newly developed New Coronavirus matrix reference material, reference material of circulating tumor DNA containing EGFR (L858R) Mutation and reference material of pathogen microorganism plasmid DNA have provided qualitative and quantitative reference standards for the accuracy of epidemic prevention and the accuracy of the existing IVD test kit and the traceability of the value.

On the one hand, the number of reference material has gradually increased. So far, there are about 2944 kinds of first-class reference materials in China, including 365 kinds of biomedical reference materials accounting for 22.7%. On the other hand, biomedical reference materials involve more and more various items in clinical testing fields.

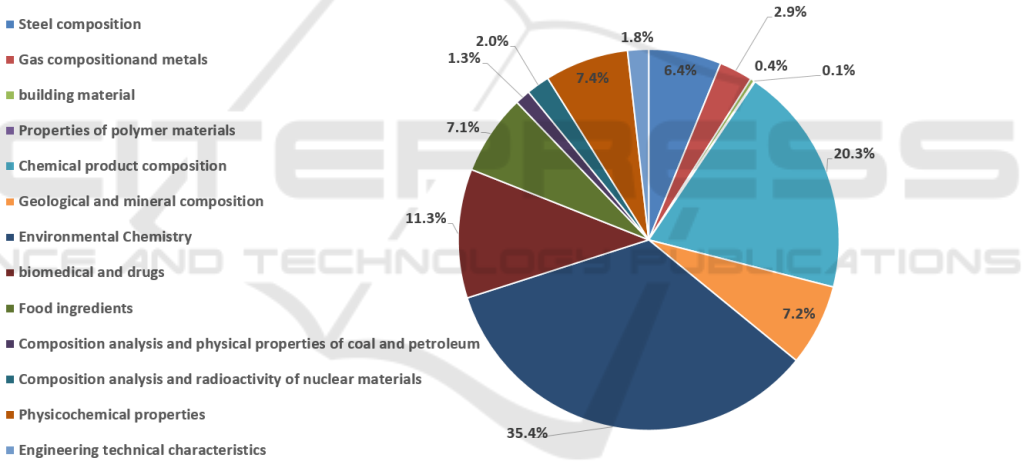

Figure 2: Distribution of reference material in China.

3.2 Organization Management

In order to apply metrological principles and reference materials to clinical medicine and health care, the International Federation of Clinical Chemistry and laboratory medicine (IFCC) was established internationally. IFCC is a global, non-political organization of clinical chemistry and laboratory medicine. It supports the development of key technologies and technical breakthrough of clinical chemical and biological reference materials, and it has made major breakthroughs in medical care. For example, the use of cholesterol reference materials can save 1.5 billion yuan per year, IFCC has become a leading organization in clinical medicine and laboratory medicine, and has improved the diagnosis, treatment level and quality of patients all over the world.

EU invitro diagnostic instrument directive requires that calibrators for in vitro diagnosis should be traceable to high-level reference materials or reference methods. In 2002, International Joint Committee on Traceability of Laboratory Medicine (JCTLM) was established in cooperation with metrology, laboratory accreditation and testing. The purpose is to establish a platform to review high-grade reference materials, reference methods and reference laboratories, and publish the results in the

JCTLM database for promoting the realization of equivalent and consistent test results.

The review of biomedical reference materials and the formulation of relevant reference methods and measurement technical specifications are mainly the responsibility of clinical medical measurement technical committee and national reference material management committee, which are responsible for reviewing reference materials and reference methods according to different division.

3.3 Interchangeability Evaluation

Due to the complexity of measurement methods and measurement system composition in individual differences of human body, there might be great differences between reference materials and actual samples, so biomedical reference materials pay more attention to the interchangeability evaluation of reference materials, The main purpose is to avoid the lack of consistency between the actual sample measurement results after the same biomedical reference material calibrates different measuring systems.

Interchangeability evaluation refers to the characteristics of reference materials expressed by the consistency between the measurement results obtained by two given measurement procedures and the measurement results obtained by another specified substance for the specified amount of a given reference material. It is more to compare with the clinical trial data to ensure that the characteristics of reference materials are consistent with the natural samples, avoid the lack of comparability of measurement results after calibrating different invitro diagnostic systems.

The interchangeability results of biomedical reference materials are closely related to the evaluation methods. At present, the most widely used interchangeability evaluation schemes are ep30-a, ep14-a3 and IFCC schemes.

The validity standards of samples, measurement procedures and measurement data used to evaluate interchangeability are basically similar, but the evaluation methods and judgment basis are slightly different. Therefore, appropriate sample quantity, type, sample status and evaluation method should be selected according to specific conditions to ensure the interchangeability on different in-vitro diagnostic systems.

4 DIFFICULTIES AND CHALLENGES

Biomedicine is developing rapidly at home and abroad. It's focus is mostly on the development of clinical reference materials, measurement and detection technology of measuring instruments for biological analysis, molecular biological reference materials and clinical application. Biomedical reference materials emerge one after another, and biometric technologies and methods have also been significantly improved.

Although many biomedical reference materials have been applied in biomedicine, clinical laboratory, inspection and quarantine and other fields, there are still many difficulties and challenges, such as:

1) Traceability: many characteristic values of reference materials are given in the form of mass fraction, molar concentration, etc., but there are few reference materials in non-SI units.

2) Valuation Technology: the valuation method of biomedical reference materials is complex, which requires expensive experimental equipment and consumables, and the development cost is high. Although the existing fluorescence quantitative PCR technology has been widely used, many experimenters did not evaluate the applicability of the method and optimize the test scheme in the development process. In fact, nucleic acid quality, primers and amplification efficiency directly affect the measurement results. So, it is necessary to strengthen the formulation of evaluation and preparation standards and specifications.

3) Raw materials: the raw materials of many biomedical reference materials come from blood, urine, etc., with great individual differences. It is difficult to ensure a stable source. Some enzyme active reference materials are easy to denature, which leads to the shortage of active components.

4) High-accuracy biomedical reference materials: The focus of this part is to develop peptide and protein reference materials for cardiovascular and renal disease diagnostic markers and related auxiliary diagnostic reference materials; Through high-throughput gene sequencing technology, we should study gene fragments for specific diseases, lock individual lesion genes, formulate personalized treatment plans, establish gene sequencing measurement methods, and carry out the development of high-accuracy and high-grade reference materials to ensure the accuracy and reliability of sequencing results and provide guidance for the implementation of targeted therapy.

5) Application in epidemic prevention: biomedical reference material of the viral crown of the medical crown virus has the physical structure of the virus like and the specific nucleic acid sequence of the new crown virus, and ensures the reliable biological safety and stability of the fake viral target through the gene transformation technology, so that the standard value can reproduce the process of the detection of the new crown virus nucleic acid to the maximum extent, and achieve the quality control from nucleic acid nucleic acid extraction to nucleic acid quantification. It provides accurate rulers for the results of COVID-19 nucleic acid diagnosis, and effectively reduces the probability of false negative.

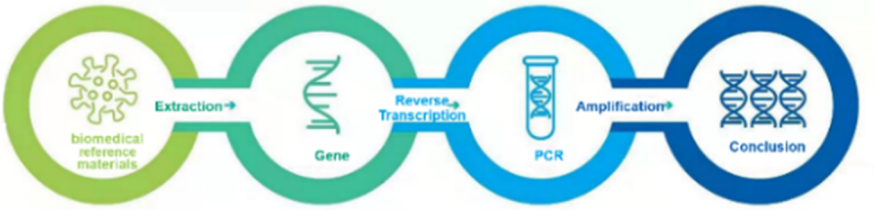

Figure 2: Process of gene transformation.

5 CONCLUSION AND PROSPECT

To sum up, it has been more than 60 years since the comprehensive introduction of medical reference materials abroad. There is still a long way to go between the research of medical reference materials and the needs of health protection, prediction and diagnosis of disease development. There are more than 1000 kinds of clinical testing items, which is obvious compared with the number of biomedical reference materials.

The purification and preparation of biomedical reference materials is difficult, and its determination components and matrix are also unstable. Now the gap of reference materials for invitro diagnostic reagents is too large to meet the needs of market testing, so the development of reference materials related to clinical testing has a long way to go.

With the rapid development clinical diagnosis demands, biomedical reference materials provide rulers and weights to meet the measurement value and accuracy, promote the upgrading and updating of national health, inspection and quarantine and intelligent medical industries and have become the gold standard for precision medicine.

In the future, we should focus on the research of reference materials urgently needed in the biomedical field, build the technical system through high-accuracy certificating technology, strengthen the research of biomedical reference materials in clinical testing, and improve the technical level of preparation, stabilization and mutual recognition.

ACKNOWLEDGEMENTS

This work was financially supported by the Foundation of China (2019YFF0216703).

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