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Review



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Editorial note：*Biopharmaceuticals are an important achievement in health research and one of the most promising industries of the 21st century，and are therefore creating new opportunities for prevention and treatment of human diseases. This article focused on the relationship of biopharmaceutical quality control and translational medicine and the application in biology，medicine and pharmacy. The link of biopharmaceutical quality control and translational medicine will develop more new biopharmaceuticals with independent intellectual properties and support a better operation of the public health care system，and also create a new area of economic growth.*

Biopharmaceutical quality control and translational medicine

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Abstract　Translational medicine aims to promote the rapid translation of basic research discoveries into the diagnosis，prevention，and treatment of diseases. The core idea of translational medicine is to create a two-way channel between basic research and clinical practice. Biopharmaceuticals are an important achievement in health research and one of the most promising industries of the 21st century，and are therefore creating new opportunities for prevention and treatment of human diseases. Research on the quality control and standardization of biopharmaceuticals is a key element of translational medicine and also a critical measure to ensure the efficacy，safety and quality control of biopharmaceuticals.

Key words　translational medicine，biopharmaceuticals，quality control，Industrialization，pharmaceutical regulation

The concept of translational medicine first appeared in 1996 in the Lancet[1]. It refers to the process that translates discoveries in basic researches into clinical practice，and covers the continuous two-way process from bench to bedside and vice versa. Translational medicine is characterized by multidisciplinary collaboration to initiate fundamental research on clinically relevant problems and rapidly application of the resulting knowledge to clinical practice. Furthermore，it also emphasizes identification of new problems in clinical practice，which can then be investigated by basic research[2,3]. Results of translational medicine research support the development of new drugs including biopharmaceuticals，and drug development and industrialization are important elements of translational medicine. Only medical products that have stable manufacturing processes and controllable qualities can provide reliable and objective evaluation for translational medicine.

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Accordingly, quality control (QC) and standards act as a critical research and development (R&D) bridge between the up- and downstream of biopharmaceuticals development, and also support and expedite the industrialization of new biopharmaceuticals.

1 Translational medicine-fueling medicine by multidisciplinary collaboration

Traditionally, medical research has primarily focused on the scientific basis that underlies various life processes. This basic science-oriented approach has inevitably led to separation between basic research, clinical practice, and development of medical products. This separation further results in a lack of relation and interaction between medical research funds and actual health care for patients. In 2003 ~ 2006, the US National Institutes of Health (NIH) provided 15 billion US dollars to fund studies on gene therapy, which produced 25 000 research papers and a consensus that "there is a long way to go before gene therapies can enter clinical use"[2]. Additionally, in the past three decades, the US government has invested approximately 200 billion US dollars in cancer research. Although the investment has rapidly advanced our understanding of the molecular mechanisms in cancers, the survival rate of patients with solid tumors has not significantly improved. In response to this failure, scientists have suggested that major human diseases such as cancer cannot be overcome through unorganized small-scale studies, and have initiated larger projects such as the Human Genome Project and the Human Proteome Project. Although these large projects are important steps toward a better understanding of human health current basic medical research remains separated from clinical practice. Overcoming this separation and better linkage of basic studies to clinical practice are crucial for the transition of current medical research.

Translational medicine provides a completely new mode for current medical research. Translation requires a combination of concept, insight and action. Instead of limiting the scope of medical research to the basic sciences, it aims to overcome existing problems in the treatment/prevention of human diseases and provide total solutions. Furthermore, through timely interactive translation between various sectors involved in health care (basic research, clinical practice, product development, and public promotion), translational medicine aims to integrate the goals and working philosophies of these sectors. Overall, translational medicine works in a patient-focused and clinic-oriented manner to coordinate activities in multiple fields and attain total solutions for the prevention/treatment of human diseases.

A key feature of translational medicine is to overcome the separation between basic research and clinical practice and create a win-win situation for both the academic community and the health care industries. In the US, the NIH is the government agency responsible for health-related research and administration. To fulfill its responsibility to manage and support the translation of discoveries from basic research to the clinic, NIH has established the National Center for Research Resources (NCRR) to provide a platform for sharing critical techniques/resources for biomedical studies and, thus, create opportunities for translating scientific innovations to improvement in public health. NCRR has successfully become a catalyst of major medical discoveries. In China, the central government recently has launched a Major Drug Innovation Project and included it as a national initiative in the 12th Five-Year Plan to expedite the translation of basic science discoveries into clinical applications.

2 Progress and trends of biopharmaceuticals

Biopharmaceuticals are produced by genetic, antibody or cellular engineering and recombinant DNA technologies for the diagnosis, prophylaxis and treatment of diseases[4]. Worldwide, biotechnology has been recognized as a key industry sector of the future. In developed countries, the growth rates of the sector are typically 8 ~ 10 times their overall economic growth rates, and >60% of biotechnology discoveries are for pharmaceuticals[5]. Therefore, biopharmaceuticals have become an area with the fastest growth and the latest technological advances.

2.1 Global development of biopharmaceuticals

The US has the leading biopharmaceutical industry in terms of R&D, range of products, and market scale. It holds 59% of the global biopharmaceutical patents, compared with 19% in Europe and 17% in Japan[6]. In 1982, the US Food and Drug Administration (FDA) approved the first recombinant biopharmaceutical: insulin. As of June 2010, the FDA has licensed 110 biopharmaceuticals, including recombinant antibodies, cytokines, hormones, enzymes, PEGylation and other modifiers[7,8]. These products have played crucial roles in the treatment of many major diseases. With clinical success of these products, the role of biopharmaceuticals in the national economy has been increasing steadily. Since 1998, the annual global sales of biopharmaceuticals have been growing at 15% ~33%. In 2009, sales had reached >95 billion US dollars (Fig. 1), accounting for 12% of the total sales of the medical industry.

2.2 Development of biopharmaceuticals in China

China licensed its first biopharmaceutical product, recombinant human interferon α1b, in 1989. The biopharmaceutical industry in China has been growing greatly over the past 20 years under funding from national and provincial science and technology programs, such as the National 863 Program. China has shown good development trends with rapid growth in the R&D and industrialization of biopharmaceuticals, gradually narrowing the gap with developed countries. Since 2005, the growth of biopharmaceuticals in China has remained at >15%. The sales of biopharmaceuticals in 2009 exceeded 75 billion RMB yuan (Fig. 2). As of June 2011, the State Food and Drug Administration (SFDA) of China had issued marketing approval for 39 biopharmaceuticals, including recombinant cellular factors, enzymes, hormones, therapeutic antibodies, fusion proteins, gene therapeutics, and genetically engineered vaccines[9].

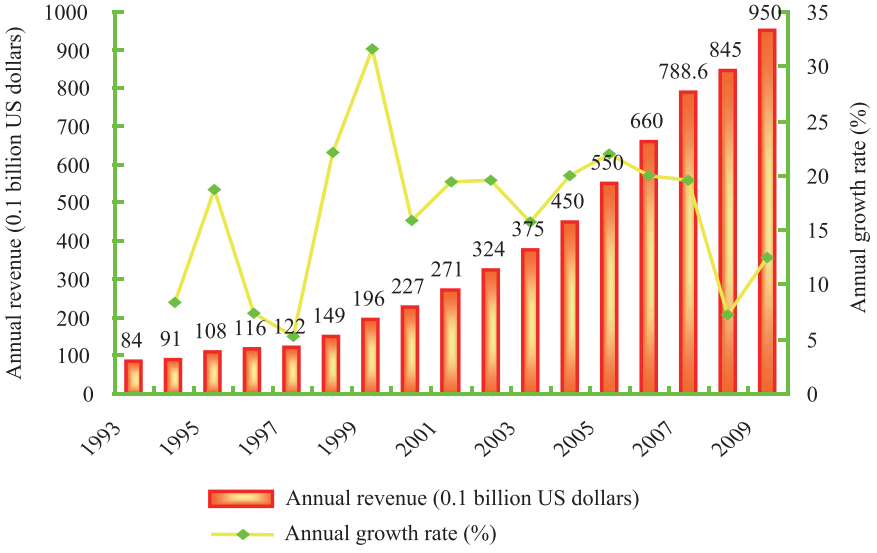

Fig. 1 Growth of the global biopharmaceutical market 1993 ~2010

2.3 Trends in biopharmaceutical development and hotspots

The indications for approved biopharmaceuticals include traditionally difficult disorders such as renal anemia, leukopenia, organ transplantation rejection, dwarfism, myocardial infarction, hepatitis B, hepatitis C, multiple sclerosis, and infertility[10]. Currently, the following six categories of biopharmaceuticals have the highest sales revenues: antibodies for cancer treatment, antitumor necrosis factor-α antibodies (targeting autoimmune diseases such as rheumatoid arthritis), erythropoietin (EPO), insulin, β-interferon, and coagulation factors. These six categories now account for >75% of the total biopharmaceutical market. With the exception of insulin, most key biopharmaceuticals are produced by eukaryotic mammalian cells such as CHO cells. In the past few years, therapeutic antibodies have shown rapid development. With clear targets and well-documented efficacies, therapeutic antibodies now have the largest proportion among the biopharmaceuticals approved by the US FDA. Consequently, they have the largest market share. In 2010, among the top 10 medicines with the largest global sales revenues, five were biopharmaceuticals and were all therapeutic antibodies. Their accumulated revenue has reached 40.9 billion US dollars[11].

The National 11th Five-Year Plan of China serves as a key transition for the innovation of Chinese pharmaceutical products. The Chinese government has invested 6.6 billion RMB Yuan on key technologies for the innovation and development of new drugs. In addition, a fund of 24 billion RMB Yuan has been collected from social organizations. With these resources, China has supported 15 integrated technical platforms, six industrial incubator bases for drug innovation, and 448 candidate pharmaceutical products, among which, 149 biopharmaceuticals have been supported. Encouraged by this project, the Chinese pharmaceutical industry (especially the biopharmaceutical industry) has grown robustly, with >120 projects currently at different R&D phases. The developmental trend of biopharmaceuticals in China mainly focuses on candid-

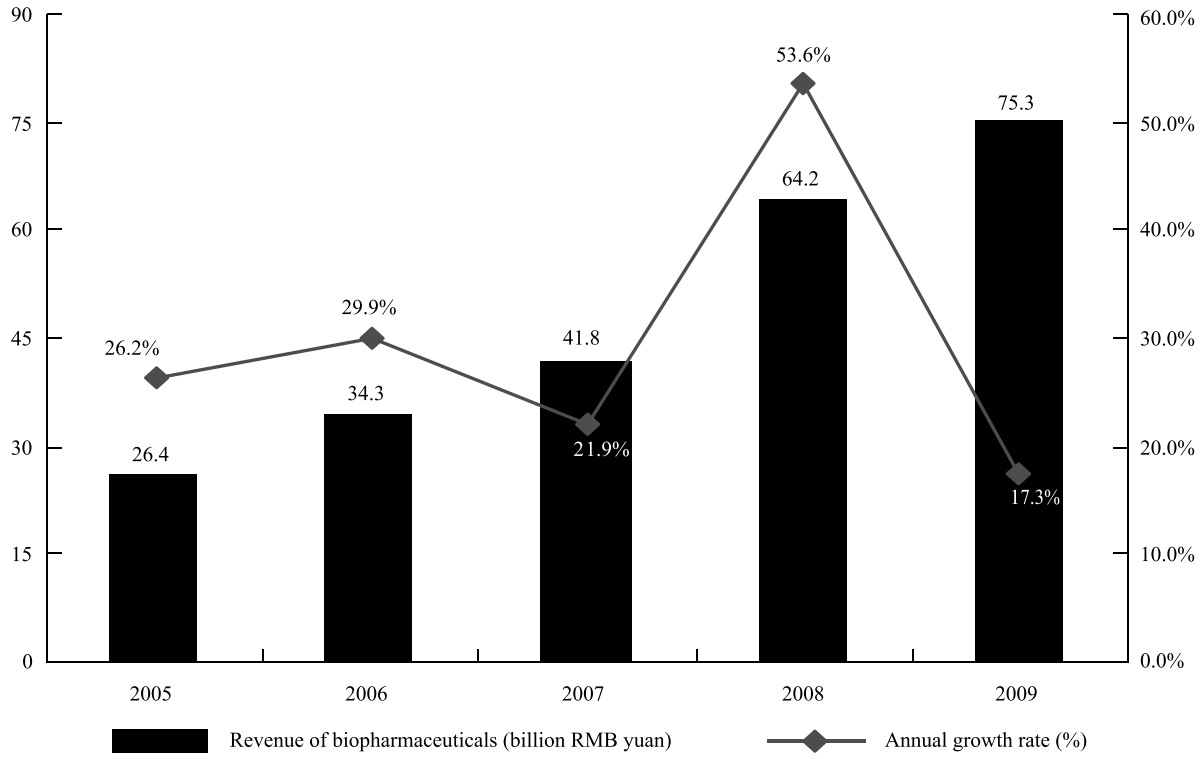

Fig. 2 Growth of the biopharmaceutical market in China 2005 ~2009

ate products that have large molecular masses and complicated structure/functions and are expressed in mammalian cells, such as recombinant antibodies. Long-acting modifications in an attempt to improve pharmacokinetic properties have also achieved breakthroughs for biopharmaceuticals such as EPO, granulocyte colony-stimulating factor, insulin, and growth hormones. With discoveries of new targets, emerging technologies such as gene therapy, cell therapy, and tissue engineering could creating opportunities for the treatment of various chronic/refractory diseases such as genetic disorders, autoimmune diseases, and nervous system diseases.

3 Roles of QC and standardization in biopharmaceutical industrialization and translational medicine

3.1 Translational medicine and innovative medical product R&D

The 20th century has seen revolutions in the medical sciences. The discovery of penicillin has effectively controlled various infectious diseases such as pneumonia and meningitis. The clinical use of Bacille Calmette-Guerin and streptomycin has substantially reduced the mortality of tuberculosis. Discovery and synthesis of critical nutritional factors (e. g. vitamins and trace elements) have fundamentally reduced the occurrence of malnutrition. The successful development of vaccines has revolutionized the prevention of many traditionally devastating human diseases, as demonstrated by the successful eradication of smallpox and effective control of poliomyelitis. More recently, two breakthroughs in surgical techniques, coronary artery bypass and organ transplantation, were established in the 1960s. In the 1990s, gene therapy was introduced for genetic diseases, such as severe combined immunodeficiency. The interaction of chemistry, physics and imaging techniques with health sciences has resulted in the invention of many key medical technologies, such as electron microscopy, endoscopy, computed tomography, positron emission tomography, and nuclear magnetic resonance imaging. These technologies have revolutionized the diagnosis and evaluation of diseases. Although technical innovations have played deciding roles in these medical revolutions, translational medicine has also made a significant contribution to the acceptance of the innovations by promoting the interaction between basic research, clinical practice, product development, and public promotion.

3.2 Biopharmaceutical QC and translational medicine

With advances in medical technologies and increasing understanding of QC, the concept of quality by design has been widely accepted. The premise of Quality by De-

sign (QbD) is that the quality of pharmaceutical products should be based upon an understanding of their biology, mechanism of action (MOA), and safety. The manufacturing process should then be developed to meet the desired quality attributes of the products. Although testing product quality after manufacture is an essential element of QC, it should be conducted to confirm the desired product attributes and not to simply reveal the outcome of a manufacturing process. The ICH Q8 guidelines clearly state that quality cannot be tested into products; that is, quality should be built in by design. This idea emphasizes the importance of designing quality research according to the characteristics of products, and also highlights the interaction between basic research and application—a key element of translational medicine.

Under the support of the National High-tech Research & Development Program ("863 Program"), China has rapidly narrowed its gap with developed countries with respect to biopharmaceutical development and industrialization. Within a short period and starting from almost zero, China has successfully started development and industrialization of biopharmaceuticals, and has initiated transition from imitation to independent innovation. Experiences in China demonstrate that effective QC of biopharmaceuticals is crucial for ensuring their efficacy/safety and successful approval for marketing. As opposed to chemical drugs, biopharmaceuticals are associated with a relatively short history and limited studies. Also, the complexity of protein structures leads to variations and diversities in their physical and chemical properties, as well as biological activities, which sets challenging requirements for various analysis and detection methods. Clearly, only products with stable production processes and excellent QC can provide reliable and objective bases for translational medicine.

Since the National Seventh Five-Year Plan, China has gradually established scientific standards and QC platforms for biopharmaceuticals. These QC platforms are comparable with international standards. These efforts provide the SFDA with a solid scientific basis in designing policies and technical guidelines to ensure QC of drugs and their eventual safe use. Domestic biopharmaceuticals have been developed continually and have flooded the market. This phenomenon has dramatically changed the Chinese market, in which foreign products used to dominate. By doing this, the prices of biopharmaceuticals has gradually decreased, which has played a key role in protecting public health and ensuring the availability of biopharmaceuticals for Chinese patients. To date, no severe adverse events have been reported to be associated with biopharmaceuticals manufactured by the Chinese biotechnology industry. This satisfactory record demonstrates the key contribution of QC and standardization research, as an element of translational medicine, to the development and industrialization of biopharmaceuticals. Research on QC and standardization not only serves as a bridge between the up- and downstream sectors of the biopharmaceutical industry, but also helps standardize and optimize research procedures, promote innovative ability and the overall quality of biopharmaceuticals, accelerates the R&D process, and advance translation of biopharmaceutical research into products.

3.3 Examples of biopharmaceutical translation into medicine in China

Recently, Chinese scientists have discovered a series of new drug targets, such as a CUEDC2 protein in breast cancer[12], interaction of nNOS with PSD-95 in cerebral ischemia[13], and D-amino acid oxidase in neuropathic pain[14]. With advances in basic medical research in China, drug development is also undergoing profound changes. Here, we review the development of two cancer vaccines as examples of traditional medicine research in China.

3.3.1 HSP65-MUC1 fusion protein as a breast cancer vaccine

Basic studies have found that mucin C1 (MUC1) is a highly glycosylated type-I transmembrane glycoprotein that exists widely in epithelial cells in the respiratory, digestive and urogenital tracts, and mammary glands. Transcription and translation of the MUC1 gene are markedly increased after the cells undergo cancerization, and cancer cells (e.g. breast and ovarian cancer) accordingly express an abnormally high concentration of MUC1 protein. Therefore, inducing MUC1-specific cytotoxic T lymphocytes is a potential treatment for breast cancer. Heat-shock proteins (HSPs) are a family of highly evolutionarily conservative intracellular proteins that are closely related to the immune response in humans. HSP65-MUC1 is a fusion protein produced by fusing the genes of mycobacterial HSP65 and MUC1, followed by production using genetic engineering. After vaccination with HSP65-MUC1, the host is stimulated to generate cytotoxic T lymphocytes and specifically kill MUC-1-positive cells, such as those in breast tumors. Pharmacological studies have demonstrated that HSP65-MUC1 vaccines can suppress the growth of tumors in mice and extend the life of mice already having tumors. Moreover, the vaccine can even induce the host to generate memory T cells to prevent tumor metastasis and recurrence. After establis-

hing the pharmacological effect of this promising vaccine, accurate evaluation of its quality (particularly its biological activities) is a crucial requirement for successful completion of druggability evaluation, determination of an appropriate pilot production process, and approval for clinical trials. Standardization studies have been launched to determine the optimum QC techniques. Based on the ability of HSP65-MUC1 to induce CD86 upregulation in peripheral immature dendritic cells, a flow cytometry method using fluorescence-labeled monoclonal antibody has been developed to quantify the relation between the dose response between HSP65-MUC1 and CD86. The method features a simple operation, short analysis cycle, and excellent reproducibility. Under effective QC by this method, this vaccine has passed quality verification and has been licensed for clinical trials.

3.3.2 Recombinant human neu epitope peptide

Preclinical studies on tumor formation have revealed that ErbB2 and ErbB3, members of the epidermal growth factor receptor (EGFR) family, are closely related to neovascularization, and the infiltration, metastasis, chemotherapy resistance, and prognosis of tumors. Recombinant human neu epitope peptide 12 is a fragment of the extracellular section of ErbB3 receptor expressed by *Escherichia coli* through recombinant DNA technology. It was evaluated as a candidate cancer vaccine administered via subcutaneous injection. The recombinant peptide can induce the host to produce antibodies that bind specifically to ErbB3 and thus block its heterodimerization with ErbB2 and, furthermore, suppress the proliferation of cells with high expression of ErbB2. It is expected to be used as an adjuvant therapy for tumors that actively express ErbB3, especially for patients with early to late breast cancer or after surgical treatment. Based on the mechanisms of this recombinant peptide, transgenic mice carrying an ErbB2 gene have been developed for preclinical QC. The mice were confirmed to be an excellent animal model for this purpose, because they expressed the tumor antigen while remaining alive and responded sensitively to human recombinant neu epitope peptide 12. The pharmacological activity of the recombinant peptide product was evaluated with the model by monitoring the titer of ErbB3 antibody. The method ensured a successful evaluation of its druggability and subsequent approval for clinical trials.

4 Concluding remarks

Population and health are major challenges to China's efforts towards building a more prosperous society. Biopharmaceuticals, as the most promising high-tech industry in the 21st century, have created more safe and effective approaches for the prevention and treatment of diseases. Many cases indicate that QC and standardization research can effectively expedite the translation of basic medical discoveries to clinical practice. Continuous identification of targets and candidate drugs is providing new possibilities for medicine. With further advance of translational medicine and biopharmaceutical QC and standardization, more new biopharmaceuticals with independent intellectual properties will be developed. These new drugs are expected to support a better operation of the public health care system, and also create a new area of economic growth.

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