Research on the Optimization of the Registration Classification of Biological Products in China

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Abstract

Objective To provide a theoretical basis for the adjustment of the registration classification of China's biological products, and to establish a continuously improved registration classification system. **Methods** Based on literature research, the specific classification methods, classification principles and considerations of biological registration in China, the United States and the European Union were studied to form a complete comparative analysis. **Results and Conclusion** It is recommended that the division between therapeutic and preventive use should be removed from the registration classification of biologics. The therapeutic, preventive and diagnostic use of the product should be limited as part of the product specification, and the registration should be classified according to the development of biotechnology, innovation, modification and bio-similar drugs. In addition, the supervision of registration of advanced therapeutic products should be different from that of traditional biologics.

Keywords: biological product; registration classification; classification principle; consideration factor

According to the "Classification of Biological Products and Reporting Requirements" (No. 43 of 2020) [1], a biological product is a preparation made from microorganisms, cells, animal or human-derived tissues and body fluids as the starting material through biological techniques for the prevention, treatment and diagnosis of human diseases. As science and technology continue to advance, biologics are rapidly evolving and the functions of biologics for therapeutic and preventive purposes are gradually overlapping. With the continuous development of biotechnology, more innovative biologics are declared and marketed. Equating preventive biologics with vaccines actually narrows the scope of preventive biologics. At present, monoclonal antibodies and human immunoglobulin as representatives of passive immune preparations have been marketed. In addition, some preventive monoclonal antibodies for healthy people have been approved for marketing. However, under China's current registration classification of biologics, there is no registration path for the above mentioned innovative biological products even if they are approved for marketing as special cases. They may not be used in disease control and prevention institutions, and it is illegal to use them in medical institutions. In addition, therapeutic vaccines are currently managed according to drugs, but the product properties are very different from those of chemical drugs, and the registration review does not match the properties of drugs.

This paper compares the classification of

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biological products at home and abroad with an aim to making feasible suggestions for optimizing the registration and supervision of biologics and establishing a continuously adjusted and improved classification system for the registration of biologics in China.

1 US biological products registration classification

1.1 Definition of biological products

Biological products are regulated in the United States under the "Public Health Service Act" (PHSA). In 2009, the "Biologics Price Competition and Innovation Act" (BPCIA) amended the definition of "biological products" to include viruses, therapeutic sera, toxins, antitoxins, vaccines, blood, blood components or derivatives, allergen products, proteins (other than any chemically synthesized peptides) or similar products used to prevent, treat or cure human diseases or its derivatives (or any other trivalent organic arsenide) [2].

On December 12, 2018, the FDA issued a "Proposed Rule" interpreting the category of "protein (other than any chemically synthesized peptide)" in the definition of "biological products" [3]. The FDA interprets the term "proteins" to mean any alpha amino acid polymer with a well-defined sequence and a size of more than 40 amino acids. There are several definitions of "peptide" in the scientific literature. Some definitions are broad (e.g., a peptide is any amino acid polymer) and others are narrow (e.g., a peptide is an amino acid polymer consisting of fewer than 100 amino acids). According to the FDA, a narrow interpretation of peptide is most appropriate in this context because it excludes other reasons and avoids exceptions to the broader category of describing "proteins". Therefore, the FDA interprets the statutory exclusion for "chemically synthesized peptides" to mean any molecule made entirely by chemical synthesis and consisting of greater than 40 amino acids but less than 100 amino acids. Except in the case of chemically synthesized peptides that meet the statutory definition of "biological products", such molecules would otherwise be regulated as small molecule drugs under FD&CA.

In 2020, the "Further Consolidated Appropriations Act" (FCAA) again amended the definition of "biological products" to remove the phrase "other than any chemically synthesized peptide". The FDA issued a final rule interpreting the definition of "biological product", which became effective on March 23, 2020. The FDA further elaborated this concept as follows [4]: Biological products as regulated by the FDA for the diagnosis, prevention, treatment and cure of diseases and conditions, are usually a class of large, complex molecules and a wide variety of products. These products are often produced in living organisms, such as microorganisms, plant cells, or animal cells, using biotechnology and are more difficult to characterize than small molecule drugs. At this time, no change in interpretation is required in light of the FDA's final determination that the interpretation of the statutory term "proteins" is consistent with the proposed interpretation made in 2018 and the term's usage in its "Biosimilars Q&A Guide" of 2015. However, the recently enacted FCA removes the parenthetical exception "any chemically synthesized peptide" from the statutory definition of "proteins" for "biological products" because "any chemically synthesized peptide" is no longer required and, therefore, the FDA will no longer interpret "chemically synthesized peptide". The FDA has also indicated its decision not to include structural or functional properties (e.g., folding) in the interpretation of the term "proteins" because doing so would raise questions and "lead to regulatory uncertainty and inefficiencies".

The US definition of biological products initially focused on category enumeration, which divided biologics according to the categories of viruses, therapeutic sera, toxins, antitoxins, vaccines, blood, blood components or derivatives, allergen products, proteins (other than any chemically synthesized peptides) or analog products, salvarsan or salvarsan derivatives (or any other trivalent organic arsenicals). Proteins (other than any chemically synthesized peptide) are also clearly defined, and the core of the

definition is the size of the molecular weight and the complexity of the characterization [5]. But peptides and chemically synthesized peptides are regulated according to small molecule drugs while proteins are regulated according to biologics. As people have a better understanding of biologics and the complex nature of biologics, the FDA no longer defines biologics with detailed category enumeration, but with macroscopic overview of their functional use, characteristics, biotechnology, etc. In recent years, the FDA has established a regulatory system for biologics that is adapted to biotechnology innovation and improvement, as evidenced by the continuous revision of the definition of biologics in the United States.

1.2 Registration classification of biological products

In the division of responsibilities between biological products and drugs, an "Intercenter Agreements" between Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research (CBER) authorize each center to have jurisdiction over the scope of drugs, biologics, and combination products of drugs and biologics. The "Intercenter Agreements" provide for the allocation of each center's jurisdiction over products by product category. Product categories are different categories that can be identified by physical characteristics, source materials or pharmacological properties. Examples of product categories include antibiotics, vaccines, hormones and human blood derivatives [6].

On June 30, 2003, the FDA transferred certain therapeutic biological products reviewed and regulated by CBER to CDER [7], which has regulatory responsibility for the transferred products, including premarket review and ongoing oversight.

The categories of biological products transferred from CBER to CDER review include: (1) Monoclonal antibodies for *in vivo* use; (2) Therapeutic proteins, including cytokines (e.g., interferons), enzymes (e.g., thrombolytics), and other novel proteins (including recombinant proteins), except those specifically designated for CBER regulation (e.g., vaccines and blood products); (3) Immunomodulators (non-vaccine and non-allergenic products designed to treat disease by suppressing or down-regulating a preexisting, pathological immune response); (4) Growth factors, cytokines, and monoclonal antibodies designed to mobilize, stimulate, reduce, or otherwise alter hematopoietic cell production *in vivo*.

The category of biological products reserved for CBER review contains: (1) Cellular products, including products consisting of human, bacterial or animal cells (e.g., islet cells for transplantation) or physical parts of these cells (e.g., whole cells, cell fragments or other components used as prophylactic or therapeutic vaccines); (2) Gene therapy products, where human gene therapy/gene transfer is the manipulation of nucleic acids, viruses or genetically engineered microbial applications that regulate host target cells by transcribing and/or translating the transferred genetic material, and/or by integrating into the host genome. Cells can be modified in these ways *in vitro* for subsequent introduction into the receptor, or directly into the patient's receptor for *in vivo* modification by gene therapy products; (3) Vaccines and vaccine-related products: regardless of their composition or manufacturing process, designed to induce or enhance specific immune responses to prevent or treat diseases or conditions, or to enhance the activity of other therapeutic interventions; (4) Allergen extracts for the diagnosis and treatment of allergic diseases and allergen patch testing. (5) Antitoxins, antivenoms, and venoms; (6) Blood, blood components, plasma derivatives (e.g., albumin, immunoglobulins, coagulation factors, fibrin sealants, and protease inhibitors), including recombinant and genetically modified forms of plasma derivatives (e.g., coagulation factors), blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations including radiolabeled or conjugated forms, and certain fibrinolytic agents such as plasma-derived fibrinolytic enzymes and red blood cell reagents; (7) Human cells, tissues and cellular and tissue-based products (HCT/P's). This category includes HCT/P's containing cells obtained after administration of CDER-regulated growth

factors, cytokines or monoclonal antibodies by the *in vivo* route, as well as HCT/P's that require *ex vivo* manipulation to obtain them by the *in vitro* route.

In addition, there are combination products that consist of a biological product with a medical device and/or pharmaceutical component. However, these products are not clearly identified. Combination products are assigned to the relevant center for review and regulation based on the primary mode of action of the product [8]. When the primary mode of action of a product can be attributed to a biologic assigned to a CDER, the product is reviewed by the CDER. Similarly, when the primary mode of action of a product is attributed to a biologic assigned to a CBER, the product is reviewed by the CBER.

2 EU biological products registration classification

2.1 Definition of biological products

Dir.2001/83/EC Appendix I Part I defines a biological product as a product containing biological substance, which is a substance derived from a biological source, the quality of which requires a combination of physical-chemical-biological measurements and production processes and controls to characterize and determine. Examples include recombinant proteins, monoclonal antibodies, human blood and plasma products. Immunologic drugs and advanced therapeutic drugs should be considered as biologics [9].

2.2 Registration review of biological products developed by traditional biotechnology

The drug registration regulation Reg. (EC) 726/2004 Article 3 (1) provides that biologics developed using one of the following biotechnological processes should be authorized by the EU centralized procedure, and not be able to use other approval procedures. Biotechnological methods include: DNA recombinant technology; Regulation of expression of genes encoding biologically active proteins in prokaryotes and eukaryotes (including transformed mammalian cells); Hybridoma and monoclonal antibody methods.

The European Medicines Agency (EMA) has seven scientific committees and a number of working parties and related groups that are responsible for the scientific review of the EMA. Biologics developed with traditional biotechnology are reviewed by the EMA's Committee for Medicinal Products for Human Use (CHMP). The Biologics Working Party (BWP) advises on all matters directly or indirectly related to the quality and safety aspects of biological and biotechnological medicines.

2.3 Registration review of advanced therapy biological products

With the rapid development of cutting-edge cellular and biological technologies such as stem cell therapy, gene therapy and tissue engineering products since the beginning of the 21st century, new treatments and products have emerged. Although these technologies and products offer great hope for diseases and human dysfunctions that cannot be solved by the current medicine. At the same time, these products have attributes that clearly distinguish them from traditional chemicals and biologics, such as novelty, complexity, technological specificity, high variability, and the ability to be produced only in small quantities. Therefore, it is clearly impractical to evaluate such products through the method of evaluating traditional drugs.

In 2007, the European Parliament and Council of the European Union issued a special regulation for advanced therapy medicinal products (ATMPs) "Regulation (EC) No 1394/2007", which came into force on December 30, 2007 [10]. The regulation requires the EMA to adopt a centralized procedure for authorizing all ATMPs and to establish an Committee for Advanced Therapy (CAT) responsible for assessing the quality, efficacy and safety of ATMPs [11], and for keeping track of scientific progress in the relevant fields.

ATMPs are divided into the following three categories: (1) Gene therapy medicinal product

(GTMP); (2) Somatic cell therapy medicinal product (SCTMP); (3) Tissue-engineered product (TEP). ATMPs can be combined with biomaterials, scaffolds, substrates and other medical devices to form combined advanced therapy medicinal products (cATMPs) [12]. The EMA emphasizes that for safety reasons, products that may fall within the definitions of GTMP. SCTMP and TEP should be considered as GTMPs, and products that meet the definitions of both SCTMP and TEP should be preferred as TEPs.

CAT, as an interdisciplinary committee, has members with professional backgrounds in cell therapy, gene therapy, tissue engineering, bioengineering, medical devices, pharmacovigilance, risk management, ethics, etc. In addition to the expert members listed above, CAT has members representing clinicians and patients, respectively. Because the CAT is central to the review of ATMPs, the CAT typically forwards draft review comments to the CHMP, which then decides to recommend or not recommend the drug for approval by the EMA based on the CAT's opinions.

The EMA has several working groups that support the review of ATMPs, including the Scientific Advisory Working Group (SAWP), which addresses scientific issues related to the field of ATMPs, and the Innovation Task Force (ITF), which engages experts from relevant committees and working groups as needed to support early communication between industry and academic institutions on innovative technologies or products for medical development, such as early communication of ATMPs products, to provide path-to-market recommendations early in development, and to keep abreast of the progress of innovative drug development so as to be ready for review [13].

3 Differences in registration classification of biological products by country

The international classification of biological products takes into account factors such as the source of production, biotechnological sophistication, molecular size and complexity of characterization, with the exception of China, which classifies biologics into therapeutic, preventive and diagnostic for registration purposes, see Table 1. The EU adds the classification of ATMPs.

Table 1 Registration classification and classification principles of biological products in various countries

Country	Registration classification	Classification principle
China	Biological products for therapeutic use; Biological products for prophylactic use, i.e. vaccine-based biological products (vaccines for immunization planning and non-immunization planning); *In vitro* diagnostic reagents managed as biological products	Distinguished by therapeutic or prophylactic use; Biological products for prophylactic use are equivalent to vaccines
US	CBER: Cellular products; Gene therapy products; Vaccines and vaccine-related products; Allergen extracts; Antitoxins, antivenoms and venoms; Blood, blood components, plasma derivatives; Human cells, tissues and cell-tissue products CDER: Monoclonal antibodies; Therapeutic proteins (except vaccines and blood products); Immunomodulators; Growth factors	Molecular size: Large and complex; Characterization complexity: Difficult to characterize
EU	CHMP: Drugs derived from biotechnological processes such as genetic engineering (including monoclonal antibodies) CAT: ATMP: (1) Gene therapy products; (2) Somatic cell therapy products; (3) Tissue-engineered products	Classification according to traditional biologics and advanced therapies Considerations: Novelty, complexity, technical specificity, high degree of variability; Small batch size

4 Thoughts and suggestions on optimizing the registration classification of biological products in China

4.1 Classification of registrations according to the development of biotechnology, innovation, improved products, and bio-similars

It is proposed that the categories for the registration of biological products should no longer be divided between therapeutic and preventive use. Besides, their therapeutic, preventive and diagnostic aspects should be limited as part of the product specification. The essence of science lies in classification, and a correct and meaningful classification should consist of a complete arrangement of several mutually exclusive properties, i.e. "independent of each other and completely exhaustive". The above principle should also be followed in the registration classification of biological products. It is recommended that traditional biological products and ATMPs should be classified according to the development of biotechnology and biological products (bio-similars) already marketed in China or abroad.

4.2 Different regulation for registration of advanced therapy medicinal products from traditional biologics

As ATMPs have the attributes of novelty, complexity, technical specificity, high variability and can only be produced in small batches with broad application prospects and great application value, the regulatory authorities, when regulating the registration of biological products, should distinguish ATMPs from traditional biological products. It can classify therapeutic vaccines, gene therapy products, cell therapy products and tissue engineering products as advanced therapeutic products, conducting independent technical review and early clinical development guidance for them, improving the marketing authorization pathway and procedures at the registration stage of advanced therapeutic products, and formulating relevant laws and regulations, technical guidelines and a series of regulatory strategies. This will enable advanced therapeutic products to be reviewed in a reasonable and efficient manner so that they can be applied to patients as early as possible.

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