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Fifty years of advancing biologicals and beyond

This year, 2023, the journal ***BIOLOGICALS*** (formerly JOURNAL OF BIOLOGICAL STANDARDIZATION, JBS, until 1989) marked 50 years of advancing the development, manufacturing, quality control, safety, efficacy, and regulatory aspects of biological substances used in medicine. The JBS was established by the International Association of Biological Standardization (IABS) in 1973, under the leadership of Dr. Frank T. Perkins, and Professor R. H. Regamey as founding editors, to encourage advancement of the standardization of biological substances. At that time, Dr. Perkins was the President of the IABS and Chief of the Biological Standardization Unit at the World Health Organization (WHO). Prof Regamey held the chair of microbiology at the University of Geneva, Faculty of Medicine and, with Dr Perkins, was a co-founder of the IABS. Later, Dr Frank Sheffield (NIBSC, UK) joined Dr Perkins as Co-Editor of the JBS in 1981. When Dr Perkins died in office in 1984, Dr Sheffield became Editor in Chief.

Vaccines were among the first biological substances, originating with the practice of variolation in the 18th Century and which led to the development of smallpox vaccine in 1798 by Edward Jenner. Rabies vaccine developed by Louis Pasteur in 1885 followed. Advances in microbiology during the 19th Century, and development of antitoxins against diphtheria and tetanus by Emil von Behring and Shibasaburo Kitasato, respectively, led to the founding of major vaccine manufacturing facilities around the world at the end of the 19th and beginning of the 20th century to produce the first biological substances, mainly vaccines and antitoxins on a large scale. The complexity of these biological substances, and their inability to be adequately characterized by traditional physicochemical methods alone, led to the birth of biological standardization in the late 19th century spearheaded by Prof Paul Ehrlich in Germany. This work led to the development of international standards for diphtheria antitoxin, tetanus antitoxin, and insulin by Sir Henry Dale in the UK during the early 20th century. Defining an international standard for insulin in International Units (IU) in 1925 enabled the widespread manufacture and clinical use of safe and effective insulin products worldwide. Likewise, defining standards for diphtheria and tetanus antitoxins in International Units (IU) in 1922 and 1928, respectively, was a major milestone in identifying the protective levels of antibodies for tetanus and diphtheria as a serum level of 0.01 IU/ml of antitoxin. This led to advances in biological standardization with written standards to control these and new biological substances. The success of vaccine development and manufacturing around the world has been due in large part to biological standardization, both International physical and written standards. Indeed, the availability of safe and effective vaccines of consistently good quality, underpin the success of immunization programs worldwide.

The manufacture of complex biological substances used in medicine starting in the late 19th century led to the beginning of the regulation of pharmaceutical products, for example with the enactment of The Biologics Control Act in 1902 in the United States (US) after a tragedy with deaths due to injection of contaminated diphtheria antitoxin and smallpox vaccine. Similar procedures for the regulation of such products were established in other countries. In the United Kingdom, the National Institute for Medical Research (NIMR) was established in 1913/14 with Sir Henry Dale as Director and included the regulation and standardization of biological products. This function was partially taken over by the National Institute for Biological Standards and Control (NIBSC) in 1972. Initially, biological international standards were developed under the League of Nations and held and distributed by two Custodian Laboratories, the MRC/NIBSC in the UK, and the Statens Serum Institute, in Copenhagen, Denmark. The latter is no longer involved in these activities and biological standards held at the Statens Serum Institut were transferred to NIBSC in 1997. Currently, the NIBSC (UK) is the custodian of most WHO biological international standards.

As the manufacture and regulation of biological substances were advancing with the development of new vaccines, human immunoglobulins, and other blood products during the middle of 20th century, the Interim Commission of the WHO established the Expert Committee on Biological Standardization (ECBS) in 1946 to continue the work of the Permanent Commission on Biological Standardization of the League of Nations. The first meeting of the ECBS occurred in 1947 and biological standardization was established as part of the Constitution of the WHO at the first World Health Assembly in 1948. In 1955, a group of regulators, scientists and vaccinologists founded the IABS in Lyons, France. The IABS in collaboration with the WHO, regulatory agencies and biologicals manufacturers then organized numerous meetings on development and standardization of biological substances, which were immensely valuable in the field of biological standardization. The proceedings of these meetings were published, initially as Symposia Series in Immunobiological Standardization and later Developments in Biological Standardization. These publications together with the founding of JBS in 1973 became the primary source for disseminating, discussing, and resolving issues relating to the development, manufacture, regulation, and standardization of complex biological products.

The emergence of molecular biology and development of hybridoma technology for production of monoclonal antibodies in 1975 by Kohler and Milstein revolutionized the biotechnology field with the development of recombinant DNA-derived therapeutic biotechnology products in the 1980s. This led to numerous new biotechnology products supplementing or replacing traditional biologicals, blood products, and other conventional biologicals. This biotechnology revolution changed the landscape in developing, manufacturing and control of biological

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products with new innovations and technological advances in large scale culturing of microorganisms, use of mammalian and other cells for production, as well as commercial scale purification processes. Great progress was also made in the ability to characterize biological macromolecules in fine detail, all presenting new challenges in biological standardization.

More than 20 years after the production of the first monoclonal antibodies, several innovative products, including humanized monoclonal antibodies, antibody-drug conjugates, bispecific antibodies, antibody fragments and nanobodies have been developed and licensed by national regulatory authorities and are in use, or are under clinical development and coming onto the market. It took more than twenty years after the discovery of monoclonal antibodies to successfully bring these products onto the market. Similarly, it has taken almost thirty years to achieve routine use of mRNA vaccines in 2021 after the initiation of work on nucleic acid- (DNA and mRNA) based vaccines in late 1980s and 1990s. This has revolutionized the development of new vaccines. Similarly, during the past several years, new advances and developments in tissue, cell and gene therapy products have led to the provision of novel innovative products with challenges in manufacture and regulation. A large number of such products are presently in clinical development.

In 1990, Prof Florian Horaud (Pasteur Institute, France) became the Editor in Chief of JBS. To keep up with these advances and developments in biologicals and to reflect the exciting new biotechnological world, the JBS changed its name to ***BIOLOGICALS***. Dr Elwyn Griffiths (then Chief, Biologicals, WHO) became Co-Editor in Chief of the revised format of the journal for a brief time with Prof Horaud, and subsequently Section Editor. Following Prof Horaud's death in 2000, David A. Espeseth served as the Editor-in-Chief. In 2005 Prof Girish N. Vyas (University of California, San Francisco, USA) was appointed Editor in Chief of Biologicals, followed by Dr Robin Thorpe (formerly NIBSC UK) in 2015 and Dr Norman Baylor (formerly, CBER FDA) in 2021. All of them have maintained the journal's focus on key biotechnological developments, regulatory science, and new biologicals, including blood products, as well as cell and gene therapy.

The last 50 years have seen significant changes in product portfolios for biological substances used in medicine and in regulatory science, such as new technological and scientific advances in proteomics, genomics, automation in clean rooms and environmental monitoring, rapid microbiological methods, and digitalization, together with new concepts in regulations, including biosimilars and Quality by Design. Some biotechnological products now comprise the fastest growing sector of the pharmaceutical market and ***BIOLOGICALS*** (and its precursor JBS) has been part of and reflected in this transformation. The journal will continue to serve as a forum for the introduction and discussion of topics which directly impact innovation and regulatory strategy in the development and lifecycle management of biological products used to improve human and animal health globally.

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