Biological Medicinal Products

Subjects: Zoology

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Definitions of biological medicinal products (BMPs) vary depending on the source. BMPs are manufactured using complex biological/biotechnological processes involving living cell lines, tissues and organisms such as microorganisms, plants, humans and even animals.

biological medicinal products bio-similar drugs

1. Introduction

Biological medicinal products (BMPs) are a group of medicines which are developing rapidly owing to the progress of biotechnological methods. In terms of structure, these are proteins with pharmacological activity, derived from living cells or obtained by genetic engineering methods. The action of BMPs involves mimicking the function of normal animal proteins. Moreover, they act as modulators of immune response, because they mobilize the immune potential of the patient in the fight against the disease [1]. Biological drugs include the following groups: vaccines, blood proteins, toxins, recombinant proteins, monoclonal antibodies, growth hormone, insulins, erythropoietin, interferons, growth factors and interleukins. BMPs are used in the treatment or prevention of cardiological, dermatological, rheumatological and oncological diseases, Turner's syndrome, diabetes, anemia, oncological and neutropenia [2]. According to the United States Department of Agriculture (USDA), veterinary biological products include the following groups: antibody products, bacterins and bacterial extracts, toxoids, bacterin-toxoids, antitoxins, vaccines, vaccines with bacterins/bacterial extracts/toxoids, diagnostic products and miscellaneous [3]. This review is limited mainly to recombinant proteins, monoclonal antibodies and mesenchymal stem cells [approved by European Medicines Agency (EMA)], and miscellaneous group (approved by the USDA).

2. Definition of Biological Medicinal Products

The definition of BMPs has been changing with the progress of knowledge. According to the 1902 definition presented by the Food and Drug Administration (FDA), traditional BMPs include therapeutic vaccines, viruses, serums, blood, blood components, toxins and anti-toxins. According to the current FDA definition, biological medicinal products are substances obtained from living organisms (humans, plants, microorganisms, and even animals) by biotechnological methods and by genetic engineering, applied in therapy of both humans and animals [4]. The USDA defines veterinary biological products as products derived from living organisms and produced during biological processes. They are used to prevent, diagnose or treat animal diseases and function through an immune process [5]. The EMA defines BMPs as medicinal products which contain one or more active substances produced by, or obtained from, a living organism [6]. The first BMP produced through recombinant DNA technology

was insulin. This peptide hormone was discovered in 1921 and from the following year, was obtained from porcine and bovine pancreases for therapeutic purposes [7]. It is noteworthy that a one-year therapy of one patient with diabetes requires insulin isolated from 100 porcine pancreases. Without recombinant insulin, 20 billion pigs would have to be kept globally to cover the annual demand for insulin for 200 million patients [8]. The world population of pigs decreased from 766.6 million in the previous year to 677.6 million in January 2020 [9]. Owing to the progress in molecular biology and genetic engineering techniques of the 1970s, researchers could conduct studies aimed at obtaining insulin by culturing genetically modified bacteria, Escherichia coli,

and yeast, Saccharomyces cerevisiae and Pichia pastoris, (by incorporating a plasmid with the gene encoding human insulin into the genome) which resulted in introducing the first recombinant drug on the market in 1982 [10] [11]. Increasing importance of recombinant medicines is testified to by the fact that in 2019 EMA approved 66 new therapeutic drugs, 18 of which were recombinant drugs, including 11 monoclonal antibodies [12]. In addition, the FDA approved 48 new drugs, 9 of which were recombinant drugs, including 8 monoclonal antibodies [13]. The above drugs have been used to treat people. The only monoclonal antibody used to treat animals is lokivetmab (Zoetis, Louvain-la-Neuve, Belgium), marketed in 2017. Lokivetmab is used in treatment of atopic dermatitis in dogs.

In Europe the marketing authorization applications of BPMs are handled solely through the centralized marketing authorization process, which is co-ordinated by EMA (Regulation (EC) No 726/2004) [14][15]. The assessment of the quality and manufacturing data of BPMs are centered to Biologics Working Party (BWP) at the EMA, whereas the Committee for Human Medicinal Products (CHMP) has the overall responsibility of the marketing authorization applications (MAA) assessment [16]. In the USA, the FDA Veterinary Medicine Center (CVM) oversees the approval and

introduction of new animal medicines [17]. However, veterinary biologics, including vaccines for animal diseases, are regulated by the U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) [18].

In the production of subsequent biological or biosimilars, non-patented production processes must be used. The drugs received are referred to as “follow-on biologics” or “biosimilars” depending on how they were approved by the FDA. However, they are not referred to as “bioidentical” or "generic” because although they are similar, they are not identical to the reference product, which is the original biological drug, and may show differences in immunogenicity, efficacy and safety.

The term “generic” refers to drugs that are identical to the active ingredient of an innovative drug and are the result of chemical reactions, not biological processes. In addition, the FDA developed the Public Health Service Act (PHS Act), which specifies two levels of biosimilar drugs [19]. The first is biosimilar medicine, defined as a biological product that is FDA approved because it is similar to an FDA approved biological reference product and has been shown to have no clinical differences from this product [17]. The first biosimilar drug approved by EMA and placed on the European market in 2006 was the human recombinant growth hormone in the Omnitrope (Sandoz GmbH, Langkampfen, Austria) product, which is a generic drug for Genotropin. The second level, however, is interchangeable biosimilar products, defined as a biosimilar product to an FDA approved reference medicine and it is possible that they have the same clinical effect as the reference medicine and can therefore be used interchangeably [20]. However, no interchangeable biosimilar products have been approved.

3. Classification of Biological Medicinal Products

There are several groups of BMPs: monoclonal antibodies, stem cells, fusion (chimeric) proteins, recombinant proteins and antisense oligonucleotides[1][21].

3.2. Monoclonal Antibodies

Monoclonal antibodies are immunoglobulins, which specifically bind to proteins located on the surface of cells and contribute to the immune response. They act as immunosuppressants or immunostimulants [22]. The first monoclonal antibodies were of murine origin; however, when introduced to the human body, they produced an immune response against the foreign-species murine immunoglobin (HAMA—human anti-mouse antibody response). For this reason, attempts at humanization of antibodies were made to reduce their immunogenicity [1]. They resulted in obtaining

chimeric antibodies, which were in 65–90% human antibodies (the percentages relate to amino acid sequence conservation), by replacing a fixed region of the heavy and light chain of the murine antibody with similar fragments of the human antibody—that is, only the replaced regions are of murine origin. Subsequently, humanized antibodies were produced which were 90–95% human; they were obtained by leaving only the antigen-binding regions in the murine antibody molecule. Currently, fully human antibodies are available, produced by transgenic mice, in which loci of murine DNA were replaced with DNA encoding human immunoglobulins [23]. The names of monoclonal antibodies end with -ab; apart from that, the name ending identifies the antibody type: chimeric antibodies, -ximab; humanized antibodies, -zumab; human antibodies, -umab [1][21].

The monoclonal antibody (mAb) timing system has been developed, resulting in an international non-proprietary name (INN) introduced at the request of the World Health Organization (WHO) or name adoption (USAN) at the request of the American Medical Association (AMA) in the United States [24][25][26]. According to these guidelines, the name mAb consists of the prefix chosen, the target sub-element and the end of the universal core “-mab”. For monoclonal antibodies used in veterinary medicine, the target element is ‘vet’ [27].

3.2. Stem Cells

Mesenchymal stem cells (MSCs) are multipotent cells, with capacity for self-renewal and differentiation that derive from the embryonic layer of the mesoderm and under certain conditions they can differentiate into can myocytes, neural cells, osteoblasts, chondrocytes [28]. In animals, two classes of stem cells have been identified: embryonic stem cells (ESC) and adult stem cells (ASC) [29], which include hematopoietic stem cells, mesenchymal stem cells and progenitor cells [30].

In veterinary medicine, MSCs are used for treatment of tendon and ligament injuries, and joint diseases, with significant clinical relevance in horses and for orthopedic applications in dogs. Most often, MSCs are isolated from: adipose tissue, peripheral blood, umbilical cord, muscle, bone marrow, synovium [31]. The low immunogenicity of these cells suggests that MSCs can be transplanted universally without matching between donors and recipients. The transplantation possibilities for peripheral blood MSCs include allogeneic stem cells being injected from

another donor animal from the some species, autologous stem cell being injected within the same animal and xenogeneic stem cell being injected from another donor animal from another species [32].

3.3. Fusion Proteins

The molecules of fusion proteins consist of two elements which make up a structure resembling an antibody. The first part has two binding domains which recognize a specific receptor protein. The other part is the Fc fragment of human immunoglobulin and it stabilizes the whole structure. The immunogenicity of these proteins is very low [22]. The names of fusion proteins end with -cept [1][33]. However, fusion proteins are not used in veterinary medicine.

3.4. Recombinant Proteins

Recombinant proteins are replicas of natural proteins or their fragments. They act specifically through cell receptors, inducing a precise immune response. This group includes interferons, interleukins, growth factors and protein hormones [22]. The names of recombinant proteins start with prefix rhu- [1][34].

3.5. Antisense Oligonucleotide

The antisense oligonucleotide group contains few drugs. These are short synthetic molecules, 12–30 nucleotides long, whose mechanism of action involves inhibition of gene expression as a result of blocking the relevant matrix RNA (mRNA) by an external complementary fragment of RNA, which binds selectively with mRNA of the gene of interest, blocks it and, in effect, prevents production of the relevant protein [35]. These drugs are indicated in selected neurodegenerative diseases [36], viral infections [37], cancers [38] and familial hypercholesterolemia [39].

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