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Introductory Chapter: Biopharmaceuticals

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1. Introduction

A biopharmaceutical (biological or biologic), which consists of sugars, proteins, nucleic acids, living cells, or tissues, is a medicinal product manufactured in extracted or semi-synthesized from biological sources like humans, animals, or microorganisms. Different from traditional drugs synthesized from chemical processes, the majority of biopharmaceutical products are derived from biological processes including the extraction from living systems or the production by recombinant DNA technologies (**Table 1**). Transgenic organisms, especially plants, animals, or microorganisms that have been genetically modified, are potentially used to produce biopharmaceuticals.

The recombinant human insulin (trade name “Humulin”) was the first biopharmaceutical approved for human therapeutic uses and marketing in 1982. Currently, biopharmaceuticals have been extensively used as therapeutic agents such as vaccines, whole blood (or blood components), immunosera, antigens, hormones, cytokines, enzymes, allergens, cell therapies, gene therapies, tissues, monoclonal antibodies, and products derived from recombinant DNA, etc. For example, vaccines are used to prevent infectious diseases and some cancers; cell- and gene-based biopharmaceuticals are applied to treat a variety of diseases for which no other drugs or medical devices are available.

The European Medicines Agency (EMA) uses the specific term “advanced therapy medicinal products (ATMPs)” to refer to human medicines that are based on cells, genes, or tissue engineering. Cell therapy products (CTPs) are biomedicines containing cells/tissues that have been manipulated to change their biological characteristics, and these cells/tissues can be used to treat, prevent, or diagnose diseases [1]. Gene therapy products (GTPs) are therapeutic agents to make genetic improvement through the repair, deletion, insertion, or substitution of mutated genes or site-specific modifications for target therapies [2]. Tissue engineering is the application of a combination of cell, engineering, and material methods, and suitable factors

Source item	Extracted from living systems	Produced by recombinant DNA
Characteristic	<ol style="list-style-type: none"> 1. Some conventional biopharmaceuticals are extracted from animals or humans particularly. 2. Some biopharmaceuticals were extracted from animals, but they are currently produced by biotechnologies. For example, the therapeutic insulin previously extracted from porcine pancreatic islets is now produced by recombinant DNA technologies in the yeast (<i>Saccharomyces cerevisiae</i>) or <i>E. coli</i>. 	<p>Biopharmaceuticals produced by recombinant DNA technologies are usually one of the following three types:</p> <ol style="list-style-type: none"> 1. Substances that are almost identical to the body's own key signaling proteins. 2. Monoclonal antibodies that are similar to the antibodies produced by the human immune system against microbes. 3. Receptor constructs (fusion proteins) that are usually based on a naturally occurring receptor linked to the immunoglobulin frame.
Example	Whole blood and blood components, organs and tissue transplants, stem cells, antibodies for passive immunization, fecal microbiota, human breast milk, human reproductive cells	Blood factors, tissue plasminogen activators, hormones, hematopoietic growth factors, interferons, interleukin-based products, vaccines, monoclonal antibodies, tumor necrosis factors, therapeutic enzymes

Table 1. Major sources of biopharmaceuticals.

are added to improve, repair, or replace only part of or whole biological tissues such as bones, cartilages, blood vessels, organs, skins, muscles, etc. It also involves the use of a tissue scaffold for the formation of new viable tissues for medical purposes [3–5].

A biosimilar, also known as “follow-on biologic,” is a biologic medical product that is almost identical to a copy of an original product manufactured by different pharmaceutical companies. It is highly similar to a licensed reference product in spite of minor differences in clinically inactive components. There are no clinically significant differences between the biosimilars and the reference products in terms of the safety, purity, and potency. A generic drug is the same as a brand name drug in dosage, safety, strength, administration, quality, performance, and intended uses. It is required to take a lot of rigorous tests to ensure that the generic drug can substitute for the brand name drug. A generic drug must contain identical active pharmaceutical ingredients (APIs) with the same amount as the brand name product and be proved to be bioequivalent to the brand name drug. The substitutability or therapeutic equivalence of generic drugs has to be evaluated scientifically. If a generic drug is evaluated as therapeutically equivalent as the brand name product, it has equal effects and show no differences compared with the brand name product. Biosimilars, like generic drugs, can be manufactured when the original “innovator” product’s patent expires, and are officially approved versions of the original products [6]. However, there are many differences between a generic drug and a biosimilar (**Table 2**). Biosimilars have the same clinical effect as generic drugs but are only similar to the original “innovator” drugs as they are confirmed by validation methods. Biosimilars will not be the same as the reference products, unlike generic drugs in which the APIs are identical to the references [7]. Despite this heterogeneity, all generic drugs and biosimilars have to maintain consistent quality and effective performance throughout their life cycles [8].

Drug property	Generic drug	Biosimilar
Molecular size	Small (~150 Da)	Large (~150,000 Da)
Structure	Simple and well-defined	Complex with probable structural variations
Characterization	Easy	Difficult
Stability	More stable for storage and handling	Less stable, very sensitive to its surroundings
Production	Predictable chemical processes are used to manufacture an identical copy	Specialized biological processes are used to manufacture a similar copy
Identical to reference products	Yes	No
	At least, active pharmaceutical ingredients are identical	Minor differences in clinically inactive components are acceptable
Adverse immune responses	Lower potential	Higher potential
Frequency of quality tests in manufacturing	≤50	≥250
Clinical trials requirement for approval	Small clinical trials in healthy volunteers	Large clinical trials in patients
Discovery cost	Low or even no	Relatively high

Table 2. Comparison of a generic drug and a biosimilar.

2. Application

Biopharmaceuticals have multiple clinical applications and various advantages for disease therapy, prevention, and diagnosis.

2.1. Therapy

The therapeutic types of biopharmaceuticals mainly include recombinant protein therapy, antibody therapy, cell therapy, and gene therapy. Biopharmaceuticals are able to cure or treat diseases safely and effectively by demonstrating biological activity, and perform specific functions by acting on the disease pathophysiology. Compared with chemical drugs, biopharmaceuticals are more complex in production, have multiple routes of administration and different pharmacokinetics. Their advantages are high selectivity and low nonspecific toxicity; disadvantages include high costs and the induction of antidrug antibodies leading to decreased efficacy or deficiency in biosafety. Treatment can be optimized through the development of dosing schedules and multiple administrative routes. Additionally, the cost can be reduced by using biosimilars.

2.2. Prevention

A vaccine is the most important biopharmaceutical used for infectious disease prevention. It usually contains a biological agent that resembles a pathogen and is usually made from

inactivated microbes, live attenuated microbes, toxoids (toxins), and or part of surface antigens (subunits). Through vaccination, the burst of many infectious diseases has enormously been decreased such as measles, tetanus, and polio; some are even eradicated such as smallpox. However, the burden of noninfectious diseases such as cancers, cardiovascular diseases, metabolic diseases, and neurodegenerative diseases is significantly increasing. Currently, some vaccines are successfully applied to prevent cancers; for example, the human papilloma virus (HPV) vaccine has been approved for the prevention of cervical cancers.

2.3. Diagnosis

In addition to clinic significance in therapy and prevention, some biopharmaceuticals can be used to diagnose diseases; for example, monoclonal antibodies have been successfully applied in the diagnosis of some cancers and infectious diseases, and more are being developed [9–11]. Once monoclonal antibodies specified for a given substance are produced, they can be used to detect the presence of this substance. They are also very useful in immunohistochemistry that detects antigens in fixed tissue sections and immunofluorescence tests that detect the substance in frozen tissue sections or in live cells.

3. Perspective and challenge

For recent studies, innovative biopharmaceuticals are developing rapidly and have opened a new era for human therapy. Many researchers involve in the development of biopharmaceuticals and achieve exciting results. Biopharmaceuticals are promising for scientific perspectives and regulatory perspectives. Nonetheless, there are still some challenges including scientific issues and regulatory issues we need to overcome.

3.1. Scientific issue

Along with the advance of biotechnologies, more novel biopharmaceuticals are marketed and used for clinical application in the world. Biopharmaceuticals have been extensively applied for disease control, prevention, and diagnosis even though some scientific challenges are still unsolved. Take vaccines and gene therapies as examples to discuss as follows:

3.1.1. Vaccine

Vaccination, the administration of an antigenic material (vaccine), is considered to be the most effective strategies for disease control. Appropriate formulation and delivery of vaccines can maximize the potential advances for disease prevention. The main advantages of vaccination include the prevention in advance and the immunity for long term; the limitations are complex vaccination schedules, strict requirements for storage, and restricted routes of administration [12]. Nanotechnology is an approach to prepare a nanovaccine with the consumption and side effects significantly decreased. Through the application of nanoparticles, it is possible for vaccines to be controlled release at specific location, stable at room temperature, and have replaceable routes for administration. Vaccines based on nanotechnologies may overcome

their limitations and result in the development of painless, safe, effective, and economic products. The major challenges are the toxicity of nanoparticles and the immune responses induced by nanoparticles, though some biodegradable and biocompatible nanoparticles have been developed [12].

Biotechnologies using recombinant DNA technologies, genetic engineering, and tissue culture encompass a wide range of procedures to modify living organisms for human uses. New vaccines employing biotechnologies improve the product quality and expand the clinical applications [13]. For example, traditional vaccines are only used to prevent infectious diseases, but vaccines based on biotechnologies are being developed to prevent many noninfectious diseases such as cancers, type I diabetes mellitus (T1DM), Alzheimer disease, drug addiction, etc. [13]. In addition, therapeutic vaccines are potentially developing for both infectious and noninfectious diseases using the biotechnologies such as reverse vaccinology, recombinant subunit vaccination, recombinant protein vaccination, DNA vaccination, and RNA vaccination. The major challenge is complex vaccination schedules. The vaccines based on biotechnologies are usually only parts of microorganisms (DNA, RNA, or protein); therefore, it is required to have multiple doses to induce additional “booster” shots for full immunity [13].

3.1.2. Gene therapy

Although many CTPs have been approved for marketing in many countries and extensively used for disease treatment [1], current gene therapies predominantly exist in basic research laboratories and their clinical applications are still on trials. Despite of this, some GTPs have been approved by the EMA such as Glybera (alipogene tiparvovec) in 2012, and by the United States Food and Drug Administration (US FDA) such as Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel) in 2017, respectively. Recently, gene therapies have become possible through the advances of genetic engineering technology that enabled the manipulation of genome and the development of delivery tools such as lipoids [2, 14], viruses [2, 14], nanoparticles [2, 14], bacteria [15], gene guns [16], electroporation [17], or nanostraws [18]. Therapeutic components must be transported to targeted cells to exert a therapeutic effect. Therefore, the delivery tool is essential for drug delivery to target cells and it is very crucial to select a suitable delivery tool with specificity, efficiency, safety, and economics. However, it is challenging for the option of delivery tools due to the following issues.

1. **Specificity:** Some delivery tools are not very specific and may deliver nucleic acids to non-target cells. It is important to reduce the risk of nonspecific delivery, but the evaluation of their benefits and risks is complex.
2. **Efficiency:** Not all delivery tools are efficient enough; some of them are low in efficiency and multiple rounds of transfections are needed. Additionally, it is hard to improve and evaluate their efficiency especially in animals and clinics.
3. **Biosafety:** Some delivery tools are toxic, biohazardous, or even destructive to normal cells or recipient hosts. Some delivery tools such as lipoids, viruses, bacteria, and nanoparticles may induce vector-associated immune responses in hosts, and to overcome immune barriers is essential [14]. Consequently, it is required to verify their safety in preliminary tests.

4. **Economics:** The research and development (R&D) of delivery tools is perhaps difficult, risky, costly, and time-consuming. Consequently, researchers, funders, and manufacturers must have enough incentives to develop delivery tools. In fact, most biotechnology companies have little incentive to discover novel delivery tools because of limited revenue and highly developmental risks.

In several recent studies, encouraging progresses have been made to possibly overcome the challenges of delivering GTPs *in vivo* [19–22] (Table 3).

3.2. Regulatory issue

Biopharmaceuticals are more complex than small molecular-weight drugs due to their biological source, large molecular size, structural complexity, and environmental sensitivity. Thus, it is essential to consider specific and special regulatory issues for the research, production, clinical trials, applications, and marketing of biopharmaceuticals, though many professional regulations and developmental frameworks have already been established. Take cell therapies and gene therapies, and biosimilars as examples to discuss as follows:

3.2.1. Cell therapy and gene therapy

CTPs and GTPs have the trend to be commodified because many manufacturers are aiming at pursuing commercial interests. Commercial promotion of unsupported therapeutic uses of CTPs and GTPs has become global challenges that have proven resistant to regulatory efforts. Some unapproved or unproved CTPs and GTPs are tried on patients only according to their indefinite perspectives. Some CTPs and GTPs which clinical trials or data are still incomplete are prematurely released on the market only due to significant interests. A coordinated approach at the national and international levels focused on engagement, harmonization, and enforcement must be implemented to reduce the risks related to direct consumer marketing of unapproved or unproven CTPs and GTPs [23]. However, in some cases, some CTPs or GTPs have not yet completed their efficacy validation, but they have enough data to verify their

Challenge	Strategy
Specificity	Discovery of a specific virus such as adeno-associated viruses (AAVs)
Efficiency	Application of a combination system such as AAVs-CRISPRs
Biosafety	Combination with several factors such as smaller Cas9 orthologues, tissue-specific minimal promoters, AAV serotypes, and different routes of administration; Development of novel and safe delivery tools such as lipid nanoparticles (LNPs), AAVs, and baculoviruses
Economics	International collaboration among manufacturers and harmonization for product review and approval in different countries can raise the profits and reduce the expenses

Abbreviation: clustered regularly interspaced short palindromic repeats (CRISPRs)/Cas9 nuclease system.

Table 3. Possible strategies for overcoming the challenges for drug delivery (cited from Table 3. Potential Application of the CRISPR/Cas9 System against Herpesvirus Infections. *Viruses*. 2018 May 29;10(6). pii: E291).

safety and estimate their efficacy. For the therapy of patients, who are in serious conditions or unmet medical needs, specific CTPs or GTPs can be accessible to these patients with adaptive licensing [1]. The regulator should establish a conditional approval system in the regulation with deadline, a fast-track review, and communication mechanism to have patients in urgent needs take specific CTPs or GTPs as soon as possible.

3.2.2. *Biosimilar*

As products of living organisms, biopharmaceuticals are more complicated than small molecular-weight chemical drugs because of their sensitivity to manufacturing processes and post-translational changes [24]. Most information on the manufacturing process is not fully open to the public, because it may be proprietary or a patent. This information gap stands for a critical challenge for biosimilar developers and plays a crucial role in explaining the differences in regulatory pathways. It is required to demonstrate biosimilarity and assure that the change in manufacturing process represents no effects on safety and efficacy. The extent of the change is usually a key indicator to the analysis required to evaluate the quality. Biosimilarity exercises have been addressed differently by regulators to realize that biosimilar developers begin with fundamental differences including culture media, purification processes, and formulations [24]. Therefore, it is required to ensure that the changes do not influence the efficacy and safety of biosimilars.

Biosimilars are defined and present their financial and clinical implications in current publications, regulations, and the US FDA guidance documents [25]. Some biopharmaceuticals may be replaced with cheaper biosimilars when they lose the patent protection. However, unlike generic drugs, biosimilars are different from the reference products in structure and function. The US Biologics Price Competition and Innovation (BPCI) Act of 2009 created an abbreviated licensure pathway to allow for the development and approval of biosimilars and interchangeable reference products that are licensed [25, 26]. The US FDA can approve biosimilars via the abbreviated licensure pathway in accordance with the BPCI Act. Biosimilars approved in Europe are only composed of simple and small molecules. Complex and large-molecule biosimilars will be subjected to a more rigorous and prolonged approval processes [25]. The financial success of biopharmaceutical therapies and their patent expiration eventually result in the development of biosimilars. The pharmaceutical company has to develop complex biosimilars that mimic the original “innovator” drugs and explore analytical methods to demonstrate similarity to regulatory authorities [25]. A comment outlines the efforts of an integrated health system to ensure biosimilar accessibility and discusses the current challenges and future implications [27]. Biosimilars still confront regulatory challenges on potential implications for pricing, site of care, and pharmacy dispensing practices [27]. Generally, we believe that biosimilars are helpful to the health-care system, but their expected benefits may not be understood in the near future.

4. Conclusion

Biopharmaceuticals are very promising for disease control and prevention due to their characteristics and multiple advantages over traditional drugs. Many novel biopharmaceuticals

are being developed and may be applied for clinical application in the near future, though some scientific and regulatory issues are still unsolved. We expect research works including the discovery, production, applications, prospects, and challenges of biopharmaceuticals to gain the fruitful outcome and have a great impact over the humans. All prospects will come true and challenges will be overcome eventually if we constantly endeavor.

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