Clinical Pharmacology & Biopharmaceutics

Short Communication Open Access

Biopharmaceuticals: The New Generation Therapeutics

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Biopharmaceuticals is highly interdisciplinary in nature and involves several subjects such as medicine, plant science, biotechnology, crop science, natural product chemistry and even engineering. Biopharmaceuticals or drugs derived from the biological sources find its roots in the traditional microbial processes. More than three decades ago the recombinant DNA technology and hybridomatechnology were developed using microbes and introduced to the pharmaceutical world. These technologies enabled large scale production of biopharmaceuticals. Biopharmaceutical industry began in the year 1980 and the Escherechia coli played an important role in the industrial production of recombinant proteins and plasmid DNA for various therapeutic applications [1,2]. The manufacturing of the biopharmaceutical products advanced a great deal to the extent of production of designed recombinant proteins and development of viral vector gene therapies for long term management of disease with potential to even cure. In fact more than thirty to sixty percent of biopharmaceutical products were derived from Escherichia coli. This was mainly possible due to very short duration of the organism doubling time and the relatively faster rate of growth with potential to attain high cell densities enabling scaling up [3-5].

Hence the manufacturing and scaling up process has evolved a great deal in the scenario of worldwide increased market demand. All these biopharmaceuticals need to be essentially produced as quality products with strict adherence to guidelines of internationally recognized regulatory authorities. Biopharmaceuticals had shown great potential in the treatment of life threatening diseases including cancer. The biopharmaceutical sector has been collaborating with research institutes, Universities, and other R&D organizations for quality production along with safety and security measures. Biopharmaceuticals offer the scope of personalized medicine that provides accurate treatment in a timely manner at right dosage customized as per the individual profile without leading to any adverse reactions particularly in the treatment of the genetic diseases [6]. Modern biopharmaceuticals focus on the design and development of biological drugs and utilizing various cell lines derived from animals, plants, microbes, insects and mammalian organisms; stem cell therapy and gene based therapies.

Genetic engineering of plants has immense potential for use as large scale production of biopharmaceuticals due to efficient transcription and translation mechanisms. These plant derived proteins can be used for not only pharmaceutical purpose but also for diagnostic, industrial and veterinary use. A great deal of research has taken place in the development of vaccines, antibodies, and other therapeutic proteins. Plant based biopharmaceutical are also safe and effective and at the same time their production is cost-effective. Genetic tools are now available for transformation of plant nucleus and cytoplasmic organelles. It is now possible to engineer the plant-virus expression vectors for transient expression of vaccine proteins and other therapeutic components in plant cell and tissues. Glycosylation is the main advantageous physiological mechanism in the production of plant derived mammalian proteins. Plant based oral vaccines can be used as source of mucosal immunity. Plant based therapeutics allows for large scale production through cultivation of the entire crop and also in large scale reactors in the form of cell suspension cultures. These advantages are suitable for commercial viability and global outreach for addressing public health crisis situations [7].

One of the success stories of biopharmaceutical is the Humulin® which is the first recombinant protein used for therapeutic application for humans and is approved by FDA in the year 1982. Orthoclone® is yet another monoclonal antibody first reaching the market in the year 1986. These were followed by a several recombinant copies of natural human proteins. Fusion proteins are now being designed and improved for their enhanced functionality. Several receptor traps, immunotoxins, and peptibodies are also being developed for the development, delivering and the stability of the fusion proteins for ultraspecific targets. They function as multifunctional antibodies. These fusion proteins represent innovations in biopharmaceutical garnering a lot of interest among pharmaceutical scientists, biochemists, molecular biologist, and genetic engineers [8]. There are also plasmid biopharmaceuticals. Bacterial plasmids provide the basic framework for the design and the manufacture of plasmid products and their applications. Plasmid DNAs are being produced from *E. coli* and they have applications in gene therapy and DNA vaccinations. Recently, the mammalian cell lines and the Chinese hamster ovary cells are the most preferred protein production platforms as they are capable of producing the glycosylated proteins.

Biopharmaceutical application in cancer therapy has gained more prominence. Cancer is usually caused by the tumor suppressor gene mutations, interaction and expression of oncogenes and environmental toxicity. The gene, metabolite, cell signaling and growth have been studied in detail and such studies revealed the specific targets for anti-cancer therapies. Biopharmaceuticals such as monoclonal antibodies, non-antibody proteins, and small molecules are developed to control the progression of the tumor growth.

Biopharmaceuticals have made immense contributions in the treatment of various disease and disorders including rheumatoid arthritis, Crohn's disease, and even life threatening diseases such as cancer. These biopharmaceuticals have enabled effective and affordable treatment of several disease that were previously not possible with traditional pharmaceutical drugs. So far several monoclonal antibodies have been approved by US FDA and European Medicine Evaluation Agency. However, incomplete post translational modification of glycoprotein increases the dosage. Due to the unique nature of biopharmaceuticals they pose several risks. The use of tumor necrosis factor alpha especially infliximab has led to the wide-scale occurrence of tuberculosis. TNF alpha has a prominent role in the immune response to the mycobacterium that causes tuberculosis. Therefore inhibition

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Received August 19, 2021; **Accepted** September 17, 2021; **Published** September 24, 2021

Citation: Sayed M (2021) Biopharmaceuticals: The New Generation Therapeutics. Clin Pharmacol Biopharm, 10: 234.

of TNF alpha will lead to increase of bacilli activity and thus causing tuberculosis [9]. Patients treated with recombinant human epoetin had displayed increase incidence of pure red cell aplasia. Healthy volunteers treated with super antagonist anti-CD28 monoclonal antibody TGN1412 have showed cytokine storm reaction. Change in the manufacturing of the epoetin alpha leads to immunogenic response to endogenic molecules. Some other challenges that the biopharmaceutical industry is facing includes the supply chain management. New challenges also include the efficiency in manufacturing processes and establishment of the advanced delivery systems. Recombinant based biopharmaceuticals are mainly opposed by the immunogenicity. When introduced into the human body these biopharmaceuticals lead to immunogenic reaction producing anti-drug antibodies and their effect is thus neutralized. Therefore the detection and the quantification of antibodies will enable devise better strategies for efficient use of biopharmaceuticals. The monoclonal antibodies and the recombinant proteins have large size and are susceptible to degradation. Therefore, technologies such as microsphere controlled release technologies, post modifications using polyethylene glycol and other polymers and genetic transformations are developed for their efficient application [10]. The mode of administration of biopharmaceuticals has also been developed that include the routes of injections, transdermal oral and pulmonary delivery. Intracellular and targeted drug delivery is also being developed.

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