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Biopharmaceuticals in Modern Healthcare: Promising or Not?

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Abstract

Over the last couple of years, biotechnology has been giving many leads in different areas of production. In the pharmaceutical industry, it has led to many discoveries and innovations by birthing vaccines, killing microbes using antibiotics and developing many products of pharmaceutical importance. Having served and still serving as an alternative to the chemical approach of drug discovery and development in pharmacy, it is conspicuous that the application of biotechnology in the production and development of biopharmaceuticals could serve as a breakthrough in the development of novel pharmaceuticals. This paper aims to (i) identify and shed light on certain areas which are currently posing a threat to the development and use of biopharmaceuticals and those which may likely have a crippling effect on biopharmaceuticals in the future (ii) suggest and/or provide solutions to these problems, and (iii) identify promising areas for subsequent researches on the seemingly vast benefits of biotechnology in modern healthcare.

Keywords: Biopharmaceuticals; Biotechnology; Anti-drug Antibody; Healthcare

Introduction

The advent of biotechnology and its adoption and application in the development of products of pharmaceutical importance has paved a way for new approaches to arise in modern therapy. Biopharmaceuticals are medicinal products extracted or semi-synthesized from biological sources like humans, animals or micro-organisms. Biopharmaceuticals are therapeutic proteins possessing active ingredients which are solely biological in nature and are produced using biotechnological procedures, including recombinant therapeutic proteins (including antibodies), nucleic acid-based products and engineered cell or tissue-based products [3]. They differ from pharmaceutical products which are manufactured using chemical-based processes. The ever-increasing and widespread acceptance of biopharmaceuticals can be attributed to the many successes that have been achieved with their use. Treatments have been provided by introducing vaccines, blood products and monoclonal antibodies in cancer, auto-immunity, transplantation and inflammatory diseases [1, 2]. Following the years after the structure and function of the DNA was construed, huge efforts have been put in to develop what

is now known as "molecular biology" and there is now available technology to sequence genomes, point out irregularities in such arrangements, and relate and compare them to diseases [2]. This helps to focus drug development and create biopharmaceuticals of high efficacy. Changes in the base pair sequence of genetic material and developments arising from the activation or deactivation of genes without any change in DNA sequence can now be reproduced in concise forms in both animal and cellular models and in vivo correction of defects related to such processes in somatic tissue have been used to solve the root cause of genetically encoded disorders [2, 12]. The aforementioned innovations are products of biotechnology and it is in lieu of the arrival of biotechnology that biopharmaceuticals have been developed. The scope of this paper, however, is narrowed to biopharmaceuticals.

Materials and Methodology

All materials used in this study are available on the Google Scholar and PubMed Central databases. Materials were accessed by the authors and used as the basis for which new information in this work were developed.

Results

Challenges/Limitations

As it is with any other invention, drug development also has its own setbacks. In the development of any new drug, there is usually no linear trajectory. The degree of success that can be achieved with any new drug depends not only on its efficacy, but is also dependent—if not mainly, by the degree to which the drug can still maintain relevance amidst the many challenges which accompany its production and use. This includes showing consistency in results obtained from pre-clinical trials and providing a basis that post-clinical trials for further development would follow similar vein and be successful as well. However, due to the high affinity and specificity of biopharmaceuticals, pharmacology and toxicology are usually aimed at the same target and as target signaling is greatly dependent on pharmacokinetic exposure in blood and tissues, exposure-response correlations for pharmacologic effect and toxicity are often most appropriately carried out by employing translational model and simulation approach tools [2, 6]. This is not an ideal method to conduct such a procedure as there are always possibilities of anomalies arising from the setup and integration of tools and/or interpretation of results. This leads to errors as a biomarker-efficacy relationship principally based on observations could be erroneous [2]. Also, accurate determination of a pharmacokinetic-pharmacodynamic biomarker relationship or a pharmacokinetic-efficacy correlation seldom always fit into a clinically relevant biomarker-efficacy relationship, as variability in pharmacodynamic properties may rule out accurate prediction of individual therapy response which relies on biomarker information [2].

Another problem which has caused a drawback to biopharmaceuticals in their entirety is the Periodic Safety Update Report (PSUR)—a tool which is employed for the purpose of providing and studying global updates as per the safety experience with the use of a given pharmaceutical [3, 4]. Despite the reasonably large amount of resources spent by marketing authorization holders and regulatory authorities on the development and evaluation of PSURs, outcomes have proofed futile and are not well understood [3]. PSUR assessments have barely indicated that safety signal for a pharmaceutical may no longer be viewed as a safety concern [3, 5]. Also, another lapse that has been encountered in evaluating the role of PSURs in the safety management of biopharmaceuticals is the absence of a control group [3]. Being publicly unavailable, the evaluation of their contribution in terms of post-approval activities has further been compounded [3]. Overall, the establishment of the role of PSURs in the safe and effective use of medicines secondary to available pharmacovigilance necessities is still lacking [3-5]. Furthermore, certain problems have arisen in the knowledge management (KM) procedures for obtaining quality via a lifecycle approach for the development of biopharmaceuticals [6]. Owing to the vital part it plays in achieving effective implementation of Quality by Design (QbD)—which requires that knowledge acquired over a product's lifecycle can be employed for further improvement in-order to create a better version of the product, a thorough evaluation of Knowledge Management has become seemingly necessary [6]. In a research involving respondents who are employees of 17 major biopharmaceutical organizations, an online questionnaire was used to obtain information from the respondents as to what knowledge source they have the most experience with. 46.9% of the respondents showed to be most conversant with knowledge obtained from development studies and 34.4% identified with knowledge from manufacturing experience [6]. There was paucity in figures accounting for knowledge obtained from transfer activities or prior knowledge and this could be a limiting factor in the attainment of QbD

goals and the foundation of control strategies [6, 7]. Albeit being commended in management sectors for controlling the development trajectory of various initiatives, Knowledge Management (KM) indices still seem to be the most under-developed resource and have not been used to achieve any QbD specific goal [6, 8, 9].

Another area which presents a huge circumstance and drawback to the adequate development of biopharmaceuticals is the inadequacy and uncertainties associated with immunogenicity testing [10]. Unlike stereotypical chemical drugs where there is no immunogenicity after administration, the production of anti-drug antibodies (ADA) following treatment with biopharmaceuticals has raised doubts concerning their safety and efficacy in therapy [10]. Immunogenicity happens when the immune system detects unfamiliarity in the biological product and consequently directs immune responses against it [11]. Inasmuch as biotechnological and biopharmaceutical products and therapeutics are obtained from recombinant human protein libraries, the continuous occurrence of immunogenicity continues to show that factors other than 'unhumanness' can trigger immunogenicity [10, 12]. Further exacerbating this problem is the nature of anti-drug antibodies as they are polyclonal, possess different isotypes, bind to different domains of the drug molecule, have varying affinities and may differ between patients making them difficult to manage [10]. Another challenge encountered comes from the measurement of anti-drug antibodies as the human serum is composed of a high excess of human antibodies. In a bid to develop laboratory assay systems for anti-drug antibody detection in order to limit or eliminate the occurrence of immunogenicity, not much success has been achieved. The surface plasmon resonance (SPR) and bio-layer interferometry (BLI) methods have achieved quite a reasonable level of success in the detection of lower affinity ADA but are still inadequate in the grand scheme of things as they cause several-fold lower sensitivity, making it most likely for the occurrence of immunogenicity to be under-reported [10, 13, 14]. Regardless of the technology employed, a widespread limitation always arises in that human ADA are mostly unavailable during method development or are difficult to be employed due to paucity [10]. To counter this problem, positive controls are used (such as an animal anti-serum or a polyclonal ADA preparation obtained from the animal anti-serum and purified) to clear this limitation; yet, results obtained may not be up to par owing to the fact that human proteins are foreign antigens in other species and ADA derived from animal bind to different epitopes on the same antigen than do human antibodies [10, 15, 16].

In conclusion, another problem limiting the growth and expansion of biopharmaceuticals—and probably the most widely identified problem—is the high cost incurred in the manufacture of biopharmaceuticals. Biopharmaceuticals are usually censured because compared to small molecule drugs, they cost a lot and a majority of the population are unable to afford them [17]. This high cost required in the production of biopharmaceuticals greatly affects its development as production companies most often lay investment decisions prior to knowing the amount of capital actually required and when estimates rise subsequently, there is not much time to adjust to the change and create appropriations with the tempo of things in the international market [17, 18]. Also, the batch production method used in the manufacture of most biopharmaceutical drugs has not only turned out to be time-consuming, but also adds to the burden of high cost in production [19]. Even though the earliest recombinant biologic product was manufactured in 1982, the biopharmaceutical industry is yet to provide affordable drugs at the highest quality [19]. Inasmuch as the continuous production method may be more efficient than the batch production method, injecting capital and resources into continuous biomanufacturing tools without having achieved prior success is not appropriate business-wise and may eventually turn out creating more problems than had been at the onset [19, 20]. Seemingly, there appears to be a sort of ethical and moral constraint arising from different perspectives and motivations in different regions of the globe. These constraints probably stem from the enormous challenges tied to the growth of biopharmaceuticals. Whatever the case may be, such constraints have created a very inimical effect in the adoption of biopharmaceuticals and their expansion in such areas has (mainly) been finite.

Discussion

Solutions and/or Suggestions

This section provides solutions and in certain instances, also gives suggestions as to how to counter the problems encompassing biopharmaceuticals as mentioned in the previous section. However, it is pertinent to note that in instances where a suggestion is provided, the suggestion is simply what it is in essence—a suggestion, arising from meticulous observations by the authors over the course of time as no prior methodical research (or otherwise) has been done by the authors of this paper to confirm whether or not

such suggestions and recommendations are effectual. In trying to eliminate problems arising from inconsistencies in determining biomarkers, biomarker-efficacy relationships and pharmacokinetic-pharmacodynamic biomarker relationship for biopharmaceuticals, "precision medicine" techniques and practices should be adopted and potential biomarker outcomes from initial clinical findings may be altered at slight levels and tested so as to achieve prospects of clinically relevant biomarkers at different dose levels [2]. Also proferring, the biomarker relationship results obtained may be used primarily as the basis for which the biomarker is determined. In addressing the under-utilization of Knowledge Management (KM) in achieving QbD specific goals, a solution has been proferred which involves the application of patent-based performance data to show the scientific and technological units of the most vital element of any pharmaceutical firm—its knowledge base [6]. The performance mutables in this patent-based performance data have been identified to include: the size of the establishment, external knowledge and information flows, the domain and depth of knowledge base and the research expenditures [6]. Proferring a solution to the high cost incurred in the manufacturing of biopharmaceuticals, significant progress can be achieved by developing and installing larger manufacturing plants. The larger the plant, the cheaper the cost of producing a unit product. This implies that a single large factory would produce a given product more cheaply compared to several smaller ones. However, the development and establishment of such large plants would require a reasonable degree of injection of capital and other resources by the government, public and private research institutes and other multinational companies into the biopharmaceutical industry.

Conclusion

Researches are being carried out frequently on the subject matter of biopharmaceuticals and new innovations and discoveries are unfolding exponentially. Hence, it would be incongruous to arrive at a standpoint regarding the fate of biopharmaceuticals at this point in time. Except it is confirmed that all the prospects of biopharmaceuticals are unfavorable for its sustenance and total adoption and dependence in healthcare, it may as well be quite safe to conclude that at current, its pros are in the same proportion with its cons, and may be higher even. With the rate of advancement in technology, which is boosting the rate and quality of research, the current problems of biopharmaceuticals are most likely to be cushioned in the nearest future. However, it is imperative to still exert great efforts in making sure that the conventional mode of chemical production of drugs is given the same level of attention as biopharmaceutical drugs.

Conflicts of Interest

Authors declared they have no conflicts of interest.

Authors' Contributions

All authors contributed equally in the research and have read and approved the final version of the manuscript.

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