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Understanding Biopharmaceuticals: The Future of Medicine

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ABSTRACT

Biopharmaceuticals are novel therapeutic products developed from living systems that are manufactured using biotechnology and complex biologics. They include widely used monoclonal antibodies and hormones, as well as emerging novel treatments, oftentimes composed of complex biomolecules engineered from living organisms. These products offer a system-based and disease-targeting solutions to chronic, prevalent, debilitating diseases. Biopharmaceutical drugs make up a substantial part of the global drug market and a majority of the new drug approvals. Most developers of mammalian cell-grown biopharmaceuticals manufacture drugs via pools of static clear plastic vessels stirred to keep cells in suspension. Although extensively used, this traditional batch fed production system suffers several drawbacks and is an obstacle to meeting the ever-increasing global demand for biopharmaceutical drugs. Replacing traditional batch fed with continuous perfusion bioreactors has been demonstrated to be highly beneficial yet remains a nascent state in the industry. In order to develop a rapid and high performing continuous perfusion upstream process, there is a need to better understand the biopharmaceutical production systems and identify and characterize engineering, cellular, and perfusion design factors that could potentially influence perfusion system performance. Dissecting and modeling performance in batch fed systems is an essential first step. In this biopharmaceutical systems case study, the state of the industry regarding processes and technologies for biopharmaceutical production is described, with an emphasis on upstream processes. New bioprocess analytical technologies on both the molecular and process scale develop and adopt suitable modeling and control technologies to replace the traditional batch approach to product realization with a continuous, more efficient approach.

In the present review, advances made in plant-based bio-pharming as drug production systems are presented. The paradigm shift in the drug discovery pipeline away from the synthetic drug mentality from screening small molecules towards the bio-pharming pathways is discussed; influences that have resulted in more consideration of drug discovery and production in plants are presented. The emergence of plants as monoclonal antibody systems and drug production bioreactors are illustrated by several case studies based on collaborative efforts based on

established and emerging transgenic technologies. Potential major advantages of the biopharming paradigm in terms of the production of complex glycoproteins in a more affordable, readily available technology relative to mammalian cell and other systems are highlighted. However, the uncertainties and challenges facing such technology from competing platforms, unresolved technical problems, patent politics, regulatory issues, potential risks to human health, issues of gene escape, and animal welfare concerns are also discussed. The paper concludes with the view that the infidelity of rigging plant-based systems cannot be allowed to diminish this major opportunity for bioproduction mastery of the post-genomic era.

Keywords: Biopharmaceuticals, Biologic drugs, Pharmaceutical biotechnology, Targeted therapy, Monoclonal antibodies and Personalized medicine

1.2 1. Introduction to Biopharmaceuticals

Biologics are medicinal products manufactured using a biological process due in part to the greater complexity of protein folding and post-translational modification compared to small molecules. These medicinal products have therapeutic actual or potential uses, or both, for humans, and are classified as macromolecules with a molecular weight of more than 1000 Da, which in turn are classified as biopharmaceuticals (biological medicinal products). There are two types of biological medicinal products: biosimilars, which are highly similar by nature to the reference biological medicinal products and may differ in impurities and minor changes in the structure process regardless of how they are produced and conjugated; and biobetters, which are intended to be superior to the existing biological medicinal products in terms of quality, safety, and/or efficacy by virtue of a different process or conjugation (Faustino Jozala et al., 2016). The biopharmaceuticals market has been experiencing a continuous growth curve, accompanied by increased demand and research efforts. New therapeutic modalities continue to make strides and break boundaries of the market to provide innovative solutions to unmet medical needs. The biopharmaceuticals field is constantly experiencing new products and their newly approved biosimilars and biobetters year on year. The overall growth of the industry has led to research efforts to tackle new technologies and novel therapeutic modalities related to protein conjugates and Biomacromolecule-based therapeutics being tried out. Each new class of biopharmaceuticals has the potential to unlock newer biopharmaceuticals matching the previously approved loved product's safety, efficacy, and quality. Making such newer entrants to biopharmaceuticals could act as a solution to a problem's already received approval by regulatory agencies, with a good example being avidin conjugated biopharmaceuticals targeting biotin receptors and carbohydrates complementing proteins-based biopharmaceuticals matching their predecessors with a sugar chain substitution. Each year, the demand for regulatory entry and quality business processes between academia and industries have become relatively standardized for the legacy biopharmaceuticals approved earlier and monitored vigilantly by regulatory agencies.

1.3 2. Historical Development

The repertoire of pharmaceutical products is composed mainly of small molecules below 800 Da. These "traditional" medicines, known as small molecule drugs, are produced by chemical synthesis–the combination of selected chemical compounds leading to completed molecules. When succeeding at the elucidation of a biological mechanism, it is natural to ask if the same can

be expressed on a mammalian cell. Such question arose at the end of 1975, when the applicability of recombinant DNA technology to mammalian cells producing commercial drugs was systematically investigated, using monoclonal antibodies as an example. At that time, hybridoma-based technology was already well established, and combining the two techniques was a challenge to be faced. A variety of micro- and macromolecules produced using this technology may be regarded as biopharmaceuticals. To be parameterized as a biopharmaceutical, a compound should either be a micro- or macromolecule, biogenic in nature, and obtained by biological techniques (Faustino Jozala et al., 2016). The first kind includes naturally occurring small molecules such as antibiotics or synthetic analogues for which the biological/biogenic routes are, in principle, no longer valid. To obtain these, chemical synthesis is required. The term biopharmaceutical is reserved for those pharmaceutical products that are kinetically, usually on a long time scale, equivalent to the biological ones. Small molecules obtained by extraction from microorganisms or from either natural or synthetic small products with a similarity match probably cannot be classified as biopharmaceuticals. The definition is therefore restricted to larger molecules, such as protein-based enzymes, peptides, antibodies, oligosaccharides, and nucleic acids of natural or synthetic origin. These kinds of drugs are not widely available, and the use of oral bio-technology could ultimately improve pharmaceutical applicability. The first to obtain regulatory approval were recombinant human insulin, followed by Somatropin and Erythropoietin. Products approved by regulators can be compiled into two universal tables: products approved in a specific period that are discussed, and regulatory authorities used within each country. Currently, mAbs are fast becoming the best-selling class of pharmaceutical drugs. Preceding marketed mAbs first pioneered important technology steps. The production of mAbs as biopharmaceuticals has become a multibillion dollar business, and mAbs have transformed everyday clinical practice across many medical conditions.

1.4 3. Types of Biopharmaceuticals

Biopharmaceuticals are biologic medicines that are produced using recombinant DNA technology. They are antibodies, peptides, proteins, nucleic acids, or whole living cells, and are used for therapeutic or in vivo diagnostic purposes (Pawlowski, 2018). Biopharmaceuticals are large, complex molecules produced using live systems, such as mammalian or yeast cells. The analyte of a biopharmaceutical is a macromolecule influenced by its full-length sequence, higher order structure, and post-translational modifications. Aggregated, misfolded, or denatured biopharmaceuticals can be immunogenic and/or inactive. A biopharmaceutical is monitored at each stage of manufacturing, formulation, and distribution to provide evidence of its identity, purity, quantity, and potency.

Biopharmaceutical drugs account for approximately 20% of the total pharmaceutical market. Of the total marketed drugs, biologics and biosimilars account for approximately 12 and 8% of marketed drugs. Approximately 2,000 biopharmaceuticals and approximately 920 biosimilars are in various stages of development and are regulated by the FDA. Most of the approved biopharmaceutical products are protein-based drugs, including monoclonal antibodies (mAbs), enzymes, blood factors, and insulin. Combination biosimilar products are biologics that consist of a “reference biological product” and an FDA-approved drug product or biologic product to enhance the effectiveness of the reference product or reduce side effects. So far, no such regulated biosimilars have been approved by the FDA. However, many combination cuRNA products are

under development targeting a wide range of diseases, including infectious, genetic, and complex diseases (Tang et al., 2022).

Therapeutic proteins are proteins expressed for their medicinal properties, including mAbs, replacement enzymes, and cytokines. Protein-based vaccines include foot-and-mouth disease virus coat proteins and yeast-derived hepatitis B virus coat proteins. Protein-based therapeutics include coagulation factors, replacement enzymes, and neurotoxins. Biopharmaceuticals differ from conventional medicines in that their manufacturing requires biological systems and complex purification steps. A biopharmaceutical is considered a biomedical product composed of proteins, peptides, nucleic acids, or whole living cells. The analyte of a biopharmaceutical is a macromolecule influenced by its sequence, higher order structure, and post-translational modifications. A protein-based biopharmaceutical is synthesized after transcription of a gene into mRNA. The mRNA is translated to polypeptides containing sometimes hundreds to thousands of amino acids and then folded into the biologically active protein structure.

3.1. Monoclonal Antibodies

Monoclonal antibodies (mAbs) are produced by B cells and specifically target antigens. The hybridoma technique has made it possible to obtain pure mAbs in large amounts, greatly enhancing the basic research and potential for their clinical use. The unique properties of mAbs, such as high specificity and selectivity to target antigens, low toxicity, long serum half-life, ease of modification, and potential for humanization have made them promising therapeutic biomolecules. All clinical mAbs that are currently on the market were produced by hybridoma technology. mAb production and engineering have made great progress during the past 35 years, and numerous mAbs have been developed and approved for use in the laboratory or clinic. Currently, there are 885 mAbs that were granted patents around the world, 637 mAbs in clinical studies, 440 mAbs that are approved for clinical use, and 27 mAbs that are both approved and commercially available (Lu et al., 2020).

Therapeutic mAbs that target a wide range of diseases have been developed and extensively studied, resulting in significant sales data. Among all therapeutic mAbs on the market, 37 are mAbs for cancer therapy, and they have been collectively generating more than US$ 11 billion in annual sales (Zhu & Yan, 2011). With the biopharmaceutical market rapidly expanding, the research and development of mAb-based therapeutics are also increasing dramatically. Among all biologics that are being studied in clinical trials, 85% are mAbs or antibody-based molecules. Antibodies and antibody-based therapeutics consist of more than one-third of all new agents currently under development by biotechnology or pharmaceutical companies. Sales forecasts predict that 6 out of the world's top 10 best-selling drugs will be therapeutic antibodies or antibody fusion proteins, and the total sales of mAb-based therapeutics will approach US$ 58 billion. Thus, it is not surprising to find that mAb-based therapeutics have become the most widely studied molecules in today's pharmaceutical industry.

3.2. Recombinant Proteins

Recombinant proteins are produced for different applications in laboratory and industrial settings. Therapeutic applications have evolved into a mature field in recent years. This has influenced the way contemporary medical treatment is perceived. There are novel, targeted therapies with recombinant proteins for cancer treatment (biologically active antibodies against cancer cells'

variants). Similar strategies are taken to prevent viral diseases. These, so-called vaccines, are designed with non-infectious, attenuated, or wholly synthetic molecular variants of environmental hazards. Thus prepared, the antibodies can be infused (biologics, anti-viral serum) or the patients' immune systems may be activated (interferons or vaccines).

The above-mentioned novelties stimulated an ever greater need for innovative technologies for the description, expression, and purification of recombinant protein biopharmaceuticals. Many biopharmaceuticals are synthesized in heterologous systems. Proteins obtained from natural sources may be unsatisfactory, thus these recombinant systems, those generated on purpose, are used to obtain satisfactory yields. Often, fast-growing and easy to cultivate prokaryotic models are used: Escherichia coli or Bacillus subtilis. Those systems are open to the inclusion of DNA coding for the protein of interest (sharing a common origin and all essential transcription units). Their genome-dedicated proteolytic processing is solely an insurmountable drawback. Those limitations are avoided with more complex systems, such as yeast or filamentous fungi. Generative and postgenerative systems of eukaryotic developmental and regulatory modifications are used at the cost of yield and activity level (Owczarek et al., 2019).

3.3. Vaccines

Vaccination, human kind's most successful means to prevent infectious diseases, was documented by Edward Jenner in 1798. With vaccinations against smallpox, there are now effective vaccines against another 40 infectious diseases, including common childhood diseases, flu, travel-related diseases, close-contact diseases, and in epidemic or endemic outbreaks. Besides vaccines to control infectious diseases, a new application has emerged during the last two decades: therapeutic vaccines which aim to treat diseases rather than prevent them. This application targets vaccines against allergies, cancer, and Alzheimer's disease. The advent of modern biotechnology and recombinant DNA technology has had an enormous impact on current vaccine development. The elucidation of the molecular structures of pathogens, combined with advances in classical immunology as well as hybridoma technologies, proteomics, and bioinformatics, has led to the identification of protective antigens and innovative delivery methods. This has resulted in a shift from empirical, serendipitous, and opportunistic approaches for vaccine development to more rational approaches based on a better understanding of the biology of the host and pathogen (Jiskoot et al., 2019). Although the safety of vaccination was one of Jenner's major concerns, this has become paramount for vaccine development by pharmaceutical companies and health authorities. National governments make large investments in vaccination programs, and mass vaccination of healthy individuals with a medical intervention bears ethical responsibilities. The target group for vaccines is essentially every human being on the planet within a whole age range, although the emphasis is on young, healthy, and born children. These differences in target populations have a dramatic impact on the clinical data that need to be generated to obtain market admission for vaccines. For all ages, however, the safety of vaccination should be ensured, which is branded sufficiently as "proven to be safe for use" (Luigi Bragazzi et al., 2018). The fundamental question in vaccine design is what type of immunological response is elicited and how to design and produce peptides, proteins, and polysaccharides that, after injection, meet the requirements of immunogenicity. Two classes of immune responses can be distinguished in humans, and both should be generated in vaccine design. The first is the innate immune response, elicited by a non-specific response to general traits of pathogens. This response is mediated by innate immune cells

which first respond to pathogens. After invasion, they can take up, process, and lyse the pathogen and present factors of the pathogen on their surface. The innate immune response can also be elicited by adjuvants, and a specific, adaptive immune response can be generated.

3.4. Gene Therapies

Gene therapies involve delivering new genes to diseased cells with the goal of treating disease (Papanikolaou & Bosio, 2021). Gene therapy can be used to restore protein production, alter inappropriate protein activity, or inactivate a gene. Therapeutic genes can be infused directly into patients' tissues, and cellular vectors are concurrently treated in the lab and re-infused. Viruses can also be modified as vectors to ensure widespread transduction of target cells. Retroviral vectors often used for hematopoietic stem cell transduction must first stem cells ex vivo. While this was the approach used with gene therapeutics to market and treat disease, genome editing technologies such as CRISPR/Cas9 can be delivered as RNA/proteins or using adeno-associated vectors. This forms the next generation of gene therapies and may be employed as drugs or for cell and gene therapies.

Among the most advanced and widely clinically used gene therapeutics are on-covalently delivering RNA/proteins utilizing lipid nanoparticles. However, the oldest and most robust modalities involve using viral vectors to deliver either plasmid or parental viruses. The latter approach has been closer to a product-centric model, where all stages, from initial development to marketing authorization, have been dominated commercially by a few players who largely monopolized the field (Hong, 2012). This approach has faced scrutiny due to both the unprecedented prices of therapeutic distributaries and efforts to prevent diversion of manufacturing capacity away from high-demand products. It has also raised concerns about insufficient planning in managing the safety monitoring burden of representing numerous uncontrollable vector products.

In contrast, the plasmid industrial ecosystem is still maturing. Plasmid manufacture mirrors conventional scFv/GnG monoclonal antibodies, VHH formats. However, plasmid quality is more difficult to define, with standards lacking relative to the broader biopharmaceutical industry. Products are overly diverse, difficult to characterize, and equipment technology lagged behind the install capacity of commercial manufacture until at least the early 2020s. This mismatch has resulted in manufacturing bottlenecks for plasmid production and a sudden increase in companies specializing in producing plasmids.

1.5 4. Manufacturing Processes

Biopharmaceuticals can be manufactured in different systems based on cellular production. The mammalian production system is mainly used for humanized monoclonal antibodies and is considered for more complex proteins. The insect production system is efficient for the manufacture of complex proteins of various sizes. The yeast production system has lower molecular misfold, glycosylation, and sialylation than human proteins and is designed specifically for secretory proteins which usually form inclusion bodies in bacteria. The bacterial production system has been used to produce a biosimilar to a recombinant human growth hormone, which has a high demand of production in terms of excess protein expression. It is important to realize that there is no perfect production system and every system has its own pros and cons. By the emphasis on productivity and cost-effectivity, the first goal of manufacturing bio-similar biopharmaceuticals

is to embrace transfer of technology. Case studies will be presented in the development of a stable production cell line, process development of the mammalian production platform and a bacterial production system, along with the on-going manufacturing process optimization. To enable cost-effectively manufacture of affordable biopharmaceuticals at commercially viable and competitive prices, two themes of engineering solutions will be elaborated on the development of next generation multi-product biomanufacturing facilities and flexible biomanufacturing platforms. To realize the promise of affordable biopharmaceuticals, it is critical to understand the complexities involved in their manufacture and formulate appropriate strategies to mitigate them. Efforts will be made to share some of the strategies in the hope that they will spark further discussions and collaborations. Process analytical technologies (PATs) mainly track the critical process parameters (CPPs) at-line or off-line. To ensure desired product quality (QP), the manufacturing processes (MPs) usually undergo process development in parallel with assay development. An integrated parallel development of a total PAT system consisted of on-line monitoring, modelling and closed loop control has also been presented to minimize the raw material use, product impurity, and batch failure in cell culture processes. At-line spontaneous particle probing (SPP) has been successfully examined as a PAT candidate for monitoring of viable and dead CVB. Using its specific responses to oil, temperature, and chemical stressors, SPP has been readily integrated to the automated monitoring system for out-of-specification early warnings. A brighter window was opened to apply higher order SPP analytics for probes at 4 μm and higher sensitivity detection limits (Jacquemart et al., 2016).

4.1. Cell Culture Techniques

Biopharmaceuticals are products of novel and significant biotechnology applications. Gross products generated from these novel biological applications are anticipated to reach 270 billion dollars globally by 2014—with approximately 190 billion dollars from therapeutic proteins, including monoclonal antibodies, recombinant proteins, and glycoproteins. Major biopharmaceuticals, including therapeutic proteins, produced in mammalian cells consist mostly of glycoproteins with attached complex and mammal-like sugars, enabling proper folding, stability, and in vivo bioactivity. Other products include monoclonal antibodies (mAbs), the largest and fastest-growing class of biopharmaceuticals, accounting for nearly 25% of total biopharmaceutical sales worldwide.

In Novartis's cell culture systems worldwide, Chinese hamster ovary (CHO) cells—mainly CHO-DG44 and CHO-K1—and human embryonic kidney (HEK) 293 (HEK293/587) cells can produce varying biopharmaceuticals in commercial production. These mammalian cells have been demonstrated suitable for the high level expression and large-scale production of therapeutic glycoproteins possessing the highly desired human-like glycosylation (Butler & Meneses-Acosta, 2012).

An improved hydrogel-based system for long-term culture is reported. It can sustain the activity of recombinant CHO cells and allow a direct provision of a nutrient-rich medium for the cells without interruptions (Li et al., 2018). Process control through mass transport in the 3D hydrogel system also achieves a deterministic and homogeneous design of experiments. This hydrogel-based system will be a simple and scalable approach for extremely high density and long-term culture of protein-producing cells, and provide a new venue for mechanistic studies of cell lines with heterogeneous growth kinetics.

4.2. Purification Methods

After lysate preparation, biopharmaceutical purification is crucial, and there is often a lack of appropriate, efficient purification methods. The purification of these expressed proteins is often the bottleneck in the total cost of protein production. In recent years, an effort has been made internationally to develop novel purifying methods based on classical techniques or the refinement and modernisation of prospected ones that could handle large volumes and allow automation (Saraswat et al., 2013). Ideally, each protein to be purified ought to be subjected to a unique set of conditions with the hope that molecules with the desired properties would be selectively harvested. This should preferably be quantitative and highly selective, thereby minimizing the number of steps in downstream processing and throughput growth. A common shortfall of novel strategies in development is that they are not yet in a sufficient state of development as to be used on a routine basis; a necessity for many industries.

Over the past two decades, affinity chromatography has witnessed rapid development, and combinatorial approaches for ligand discovery are revolutionising the approach to initial purification. Nano-sized affinity probes displaying a large repertoire of ligands on phage, yeast, or MUD scaffolds have emerged as attractive alternatives to bioassay services used previously for the discovery and benchmarking of affinity ligands. Such probes can readily be multiplexed and partially purified yeast samples or cell culture and tissue extracts subjected to screening efforts for target-specific ligands and needed for commercial chimeric proteins, owing to their performance with crude extracts. These ligands can be engineered to be stable at the wide pH and temperature ranges used in the cleaning and sterilisation of affinity columns, thus simplifying their use over multiple 'upstream' and purification cycles. It is anticipated that these developments will ultimately result in reduced costs of the purification process and increased product yield.

Increasingly, in processing phospho-proteins for research use, it has become evident that mixtures of phosphotyrosyl and phosphoserine antibodies are more likely to reveal biomarkers than would be achieved with either probe set alone. A significant proportion of new mAbs policed by academics are being co-produced by major suppliers. When antibodies come to market that are appropriate for small numbers of target samples, and supply chains mature such that labelling products become validated and robust, this area may emerge and will become important for therapeutics. Where the target-related in-house expertise is weak, closed-panel assays based on comprehensive surface-plasmon resonance datasets may become widely used.

4.3. Quality Control Measures

Quality control is a broad and critical field for the manufacture of biopharmaceutical products. Throughout the production lifecycle of a biopharmaceutical, the health authority specifies and has the right to modify quality control tests to ensure a safe and effective product. At the lowest level, raw materials need to be tested for identity, purity, potency, and freedom from contamination. The resulting harvested material requires different testing to ensure the intended separation and concentration were achieved. The purification process, beginning with the starting material and including thousands of purification steps, should reduce the intent contamination by all measures to an impotent and non-immunogenic Product which should not induce an immune response (Sachan et al., 2014). The end-product should be evaluated for biological activity and homogeneity, since both guide registration.

Larger aspects of biopharmaceutical manufacture such as facility suitability, equipment calibration, reagents validity, and compliance with health authority and internal AQA standards should also be evaluated by procedures, tests, and regulations that may be ill-defined or dependent on successful initial manufacture. Because of the complexity of products and processes, almost any quality control test can have unexpected complexities or yield anomalous results. Just as the thermodynamic laws governing phase 1 chemistry remain valid through phase 112, despite observation of countless chemical failures, the principles for quality control remain valid but increase exponentially in number as production scales. AQA and production have the same basic motives and value, but the understanding, scope, and opportunities are very different, especially in the 2-3 year period most quality control staff rotate through in AQA.

1.6 5. Regulatory Framework

Biologic drugs represent a new generation of therapeutic agents with diverse clinical applications and strong prospects for the future (Ilić et al., 2012). While the growth of the biopharmaceuticals market has been stable, the dawn of new innovative molecules has attracted various businesses, particularly biotech startups, and put existing companies under pressure to maintain market share. Due to these factors, it is anticipated that there will be long-term strong growth and an influx of businesses in the field of biopharmaceuticals. Biophysical testing is important to provide industry-relevant information that can be mutually understood and industrially useful. Biopharmaceuticals are biological drugs that have been produced using biological systems and have a compound nature including high-molecular compatible polysaccharides and proteins. Unlike general pharmaceuticals, their intrinsic properties lead to new challenges in development, formulation, and production.

The challenges largely arise from the intrinsic complexity of the biopharmaceuticals. As a result, development of biologics requires specific techniques and approaches that are different from those used for general new chemical entities. Biopharmaceuticals are produced from living cells, and there are many steps that need to be carefully controlled to prevent bioprocess events that could lead to unwanted products making it to clinical testing. Biopharmaceutical development is challenging in three ways: the protein and/or glycan product becomes increasingly complex as the molecular weight increases; biological products are generally much larger than small drugs, increasing the number of states the biopharmaceutical can assume; and unlike small drugs, the folded oligomeric structures of a biological product are decided by the biomanufacturing operating conditions.

5.1. FDA Regulations

Biopharmaceuticals are becoming a vital pillar in the ongoing transformation of not only medical care but sciences in general. As these products have entered clinical practice, they have created the need for specific regulations to ensure safety and efficacy. Biopharmaceutical Novo Nordisk's Fiasp has recently entered the market, which has forced the FDA to adapt regulations for development and testing of this product (Hong, 2012). To monitor therapeutic products in vitro standards are applied to ensure successful translation to more complex testing in vivo as well as to human trials. Assays based on endogenous expression of the target protein in a relevant model system will allow for relevant safety and efficacy testing in both animal models of the disease and in clinical practices.

The FDA is the agency that has been charged by our government to ensure the safety and efficacy of all medical products sold to the public. Any innovative drug or device must be approved by the FDA before it can be sold to the public. The FDA also imposes regulations on the way a medical product is developed and tested. It is FDA's responsibility to safeguard the health and safety of the public by making certain that medicines are safe and effective, and that corporations provide accurate truthful and not misleading information about the product. The production of biopharmaceuticals hardly follows any of this. For example: Bivalent antibodies were tested for their therapeutic effectiveness against toxins A and B of C. difficile. Efficient toxin neutralization was exhibited in mouse and guinea pig models of C. difficile disease. Bivalent IgG eliminated bacteria and their toxins from the gut and also rendered the upper gastrointestinal tract free of toxins. These neutralizing IgGs and mAbs may prove valuable for the treatment of C. difficile-associated disease. mAbs against toxins A and B also proved valuable in preventing the development of C. difficile-associated disease in hamsters. These data suggest that mAbs against toxins A and B may be valuable for the immunoprophylaxis of C. difficile-associated disease.

5.2. EMA Guidelines

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), since 2005, has released guidelines, written specifically by working groups focusing on biosimilars, that deal with many aspects of biosimilar development. The comprehensive initial guideline was released in 2006, subsequently refined in 2014 to align with the new operational policies of the CHMP, and later revised in 2023. Similar versions from the Guidelines on Non-Clinical and Clinical Issues were also released in both years (Rahalkar et al., 2018).

Early in 2023, the European Commission, after collaboration with the European Medicines Agency, issued new biosimilar guidelines. These guidelines signal a shift in the EU's approach to biosimilars, with a clear focus on drawing a definitive line between innovator and biosimilar products followed by a mandate for small molecules. There are now five guidance documents that address the requirements that biopharmaceutical companies, research institutions, universities, or any manufacturer of implicated drugs have to follow before approval. The panel also suggested that there should be at least a 10% variation in the bioassay of the biosimilars (Schellekens, 2009).

5.3. Global Regulatory Challenges

Biopharmaceuticals are not just an idea of the future: they are already changing the face of medicine. The conventional "small molecule" drugs that dominate present treatments typically cost from a few pennies to several dollars to manufacture, while biopharmaceuticals differ dramatically in their manufacturing processes and therefore their costs. They are made using bioreactors: vessels filled with living cells that produce the agent that cures, blocks or alters physiological actions. The capital cost of biopharmaceutical production facilities, including the bioreactors, is measured in billions of dollars: a cost borne not by the drug companies, but by the pharmaceutical companies that sell the biopharmaceuticals.

Biopharmaceuticals may turn out to be a curse rather than a blessing. Biopharmaceutical production is huge, costing many times that of conventional drug production. The industry believes prices would fall dramatically if biopharmaceuticals were produced by small biopharmaceutical plants, with no capital costs or very low capital costs, and the biopharmaceuticals shipped to the health providers directly to inject.

Modern biopharmaceuticals are produced with excellent safety. A public health establishment more than triage is needed for the new interventions. Fully licensed providers should be independently evaluated and accredited. Changes should be made to the existing procedures for this evaluation and accreditation. A biopharmaceutical can be altered at any time by using a different culture medium for the living cells, while still claiming to produce the same biopharmaceutical by the same overall production technique. There is, as in medicine, a major failure of knowledge translation in the biopharmaceutical field. The regulatory authorities need more and better knowledge of immunology, both basic and new developments, as does every medical profession group. As a priority, there is a need for rapid training of staff with working knowledge of the key fields in the biopharmaceuticals. However, government management must attempt to hire several full-time regulatory professionals with demonstrated capacity, and from the outset of their employment ensure keeping them and developing their skills and capacity.

1.7 6. Clinical Trials

Biopharmaceuticals small, protein-based molecules produced by biotechnological processes, genetically modified organisms, or hybridoma technology. They are different from standard pharmaceuticals small molecules with a well-defined structure that can be synthesized chemically. Biopharmaceuticals include monoclonal antibodies, enzymes, hormones, blood factors, vaccines, cell-based therapies, and gene therapies. These molecules have unique therapeutic applications. Commercialization requires building manufacturing facilities, regulatory approval, formulation development for stability, and patient delivery systems. Biopharmaceuticals are predominantly parenteral and need to cross biological barriers safely while maintaining efficacy, delivery, and cost-effectiveness. Such drugs can be sensitive to temperature and pH variations, and their formulation is challenging.

The marketing application submission for a biodeveloped biopharmaceutical product is a decision that requires a great commitment of funds and human resources. Marketing applications are complicated, voluminous, multi-disciplined documents that need to be prepared carefully and beyond the usual scientific concerns or discipline(s) involved in product development and its precision measurement methodologies. Cross-discipline consultations, interactions with regulatory agencies at early major decision points, and cooperative teams are essential, especially when considering that traditional pharmaceutical products must be used in-vivo in drug-device combinations that may be patented or built on proprietary technology.

The major regulatory agencies governing biopharmaceutical development are national/regional bodies. In addition to the US agencies that develop the regulations that govern drug development and licensing, the International Conference on Harmonization (ICH) was formed in April 1990 to address the issue of globalizing such regulations. In 1996-2001, a series of guidance documents on characterization and preclinical safety evaluation of biotechnology-derived pharmaceuticals was developed. These guidances represent the current thinking on preclinical safety evaluation of biotechnology-derived pharmaceuticals (Aurigemma et al., 2005).

6.1. Phases of Clinical Trials

Pharmaceuticals for human use are drafted under U.S. Department of Health and Human Services regulation and require testing for safety and efficacy prior to licensure. Drug candidates undergo at least 3 phases of clinical trials prior to the submission of New Drug Application (NDA) to the

Food and Drug Administration (FDA) for review and approval, allowing for marketing of the new drug. Duration of support clinical studies in the U.S. and overseas has been 16-18 years from the original filing of Investigational New Drug Application (IND). There is a moratorium on product licensing during the NDA review process by the FDA that can take from 3 months to 7 years. For regulated products, safety and efficacy studies are performed on the actual product that will be marketed to potential users. Safety studies include toxicology, dosing, tolerance, and pharmacokinetic studies; efficacy studies include studies of the degree of response to drug at various doses, duration of therapy, routes of administration, and variations in method of formulation and preparation. Candidate drugs are characterized in detail (Aurigemma et al., 2005). Phase I clinical trials entail small numbers of healthy subjects (or patients) receiving graded doses of the test drug. These studies are designed to determine safety of the drug and pharmacokinetics. Such studies provide initial human data on absorption, distribution, metabolism, and excretion (ADME) of the candidate drug substance. Phase I studies on Hawaiians receiving Paraffinoil have resounded in safety problems with the drug. Understanding the full scope of drug behavior in humans is a long-term proposition. Examples of drug candidates successfully marketed include those subject to conventional Phase I studies in humans, as well as those that fell short of their intended purposes. There are practices often used to preclude human safety problems and go forward with development and clinical testing of drug candidates with safety uncertainties. Subjective ratings of well-being, desirability states, and punching response to aversive stimuli were reliably obtained during PAR at different ambient temperatures in groups of subjects that were privately administered IV bolus dextro-amphetamine doses. Substantial pharmacological effects were obtained using empirical approaches to sentence construction. Time-course estimates of amphetamine effects on the POMS vigor score provided converging evidence for the operant effects of amphetamine on the mood state of euphoria in humans. Evaluation of adrenocorticotropin (ACTH) precursors were performed on nonhuman primates as a procedure to obtain safety and toxicology data for candidate biopharmaceuticals. Indirect insights were obtained regarding immunogenicity and responsivity. The compassionate-use experience uncovered problems with the reasoning behind drug development.

6.2. Ethical Considerations

The biopharmaceutical enterprise continues to evolve, rapidly responding to new scientific challenges and developing novel technologies for research, drug discovery, vaccine development, quality control, manufacturing, and distribution. Regulatory agencies are equally challenged to stay in step with rapidly evolving science and technology. The new and exciting technologies being developed and employed in biopharmaceutical research and production, and the rapid pace at which they are being introduced, raise many ethical questions (E. Van Campen et al., 2021). These questions are raised in the societies affected by these technologies, and regulatory agencies attempt to formulate the appropriate and efficacious responses. Additionally, questions concerning how best to protect the rights and welfare of subjects and patients who participate in the processes necessary for establishing the safety and efficacy of these products have arisen in recent years.

A review of the gray and published literature reveals that many of the ethical questions being raised in the biopharmaceutical industry regarding compliance with applicable protocols, guidelines, and regulations are beyond the expertise of those reviewing them. Consequently, some new approaches are being developed to prepare biopharmaceutical industry scientists, staff, and management for

success in the increasingly complex world they inhabit. Some of these approaches have begun to involve the development of essays, position papers, and guidelines. Thus, consideration of ethical questions is becoming more formalized by committees and working groups composed of scientists and ethicists.

This paper will first clarify the intent behind the guideline you have been asked to comment upon. Next, it will review basic principles of research ethics relevant to the biopharmaceutical industry, and how each applies to the above intent. Different bioethics specialties are discrete disciplines, all relevant to the biopharmaceutical industry, which should be applied at both company guidance level and case-specific level. Consideration of bioethics norms can both facilitate compliance with existing protocols, guidelines, and regulations, and help identify questions, fears and discontents. Consequently, consideration of bioethics norms provides an essential foundation for a successful biopharmaceutical enterprise.

6.3. Data Analysis and Reporting

Publishing, reviewing, and approving biopharmaceutical data is a complicated process. The clinical trial data is analyzed, compiled, and reviewed by many people and across multiple systems. In this work, an enterprise-wide system-agnostic solution is presented that enables cross-source review of clinical data. Data from many separate sources are mapped and ingested into analytic storage for review and exploration. Review views built within the platform allow proper visualization and access to certain analytic capabilities. Management dashboards provide at-a-glance awareness of review tasks, reviewer appointments, and progress across teams. Users can analyze and explore data in a flexible interface, together with research scientists who can develop data visualizations and explores mappings of new data sources. Additionally, a DSL for reviewing clinical data is introduced, along with various views that wrap this language with graphics, widgets, dashboards, and workflows (Žagar & Mihelič, 2022). The introduction of the system is discussed, as well as efforts to make it sustainable and adoptable as new review systems are built. The initial implementation highlights the opportunity for improving the current process.

The pharmaceutical industry is known for innovation, skilled employees, and a high level of quality. Pharmaceutical companies invest a large amount of money into research and development, and their products need to comply with strict legislation and guidelines (A Farnum et al., 2019). Despite these properties, the industry is also known for being relatively reluctant to embrace changes and new technologies. It is one of the most highly regulated industries, and large changes would disrupt the well-oiled system. However, in recent years, regulatory bodies have been encouraging a shift towards more data-oriented medicine manufacturing. It is expected that the amount of data created during the manufacturing process will grow exponentially in the coming years. Medicine manufacturing processes are today equipped with a large number of sensors monitoring critical process parameters. Every product manufactured has a large amount of collected data from incoming raw materials to the final product quality. Most of this data is not used efficiently.

1.8 7. Market Trends and Economic Impact

The biopharmaceutical market is dynamic and rapidly expanding. Biopharmaceuticals, which are produced by living cells, have the potential to replace traditional medicines or act directly on the immune system. Biopharmaceuticals include a wide array of products and therapies that are

produced from or use biological or living systems, such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, drugs, proteins, and nucleic acids, as well as biotechnology-based industrial products. Research and development in the biopharmaceutical market has gained momentum with increased funding from governments and research institutions, and stringent regulations on pharmaceutical quality has sparked interest in the biopharmaceutical industry (Lalor et al., 2019).

Biopharmaceuticals, also called biological medicinal products, are medicines that include proteins, antibodies, vaccines, and other blood products. More specifically, biopharmaceuticals can be classified as monoclonal antibodies, blood factors, insulin, erythropoietin, and others. The market for biopharmaceuticals has witnessed rapid growth during the past two decades with more than 300 bio therapeutic products worldwide including many products at various stages of clinical trials. Major biotechnology companies are working toward the development of smaller and more effective medicines, which are more potent than traditional medicines. In this regard, peptides, proteins, and oligonucleotides are drawing the attention of the healthcare industry. However, the production of complex biopharmaceutical products is a challenging task, as this involves multiple procedures, platforms, and purification techniques.

The biopharmaceutical market was over USD 351.42 billion (2022), and it is expected to reach USD 668.78 billion (2030), growing at a 15.1% CAGR (2022–2030). The global biopharmaceutical market has witnessed an exponential rise and continuous expansion in its relevant capabilities. Biopharmaceuticals, as a focus area of research and therapeutic interests, have grown due to further non-explored potential applications of biotechnology in the pharmaceutical industry along with continued advances in protein structure characterization, synthesis, and model rational design. The ever-increasing biopharmaceutical manufacturing stressors, along with spectrums of complex product and process quality attributes, formulation and process parameters emphasized shift in understanding of biology and chemistry on production and purification of biopharmaceutical.

7.1. Market Growth Projections

In 2014, nearly two dozen marketed biopharmaceuticals projected to become available for sale included eight monoclonal antibodies (mAbs) indicated for autoimmune disorders, seven mAbs for malignancies, four proteins for hematological disorders, and one enzyme for lysosomal storage disease (LSD). Five of the ten top-selling biopharmaceuticals were mAbs or mAb fragments, indicated for malignancies or autoimmune disorders (M. Zhu et al., 2017). The biopharmaceuticals market is growing, indicating that this domain of business is increasingly evolving. As the industry matures, the focus on chronic illness and complex diseases will sharpen. One of the hottest therapeutic categories is mAbs and their formats. A large number of mAb candidates are in various stages of clinical trials. Furthermore, some marketed therapeutic protein products will face competition from biosimilars. On the other hand, during the transition of biologics to biosimilars, it could be beneficial to get a clearer picture of the newer entrant biosimilar protein products and addressing safety concerns while presenting itself as state-of-the-art technology (Lalor et al., 2019). The increasing sophistication of transgenic animal platforms leads the market in protein bio-manufacturing. The animal-derived biopharmaceuticals tend to include human recombinant proteins that are intended for topical application and more complicated structures such as coagulation factors and thrombotic enzymes. Most candidate drugs are monoclonal antibodies

(mAbs) of either human or humanized isotypes. The long-lived transgenic platforms have been established in a number of different species including goats, cows, pigs and chickens using various technologies. There is likely to be an explosion of commercial implementation of the more sophisticated platforms, especially goats. It is expected that together with the conventional products, the sector will offer mAbs of advanced specificity, potency and safety. However, over-specification may down-grade the early entrants.

7.2. Investment Trends

Biopharmaceutical gross annual revenue has risen dramatically since the turn of the century and frequently exceeds the revenues of top selling traditional “small molecule” drugs. There are also now dozens of government approval agencies globally, such as the US Food and Drug Administration, the European Medicines Agency, and the Japan Pharmaceutical and Food Safety Bureau. Approval of innovative biopharmaceuticals takes years of study and at least ten years from concept to market. The time constraint, coupled with the slow revenue ramp up in possibly the largest growth therapy space in the next decades, raises the unavoidable question in multiple stakeholder corners. Various Financial, Pharma and Biopharma investment approaches in the biopharmaceutical industry deserve attention as companies pursue effective strategies (J. Ahn et al., 2018). In 2014, Market exclusivity, Notice of allowance, and Complete response letter risk asymmetry threatened Biogen Idec’s billion-dollar MS drug, BG-12 was periodically reviewed before diving into execution on decision points deemed too risky. The acronyms of such points at this revenue stage are overwhelming and not wholly known. Interestingly, companies highlighted additional annual savings per drug (≥$100 M for process), and research opportunities for previously halted indication. Initial compounds may raise Byrd-Holt, followed by UK-HTB, before maturation outcompeting established drugs on share. Transition to Crude Extracts led to acquisition as CEO leaving for 2 entrepreneurs who start a new-gen company today. Expanded areas such as targeting AD with nFUS2s escaped recent wildfires but were not analyzed on fail-factors (Lalor et al., 2019).

7.3. Cost-Effectiveness Analysis

Cost-effectiveness analysis (CEA) is used by a number of governmental programs to assess new therapies as part of determining whether they will be added to a formulary, and most of the economic evaluations submitted to regulatory agencies are of this style. These programs generally use the same processes to determine cost effectiveness, but vary somewhat in what is defined as cost effective and the threshold ICER that determines a therapy as such. For example, under England’s National Institute for Health and Care Excellence, new therapies below £20,000 per quality-adjusted life year (QALY) are deemed cost effective, whereas Canada’s Common Drug Review considers drugs to be cost effective within a wider range of CAD $20,000 to CAD $100,000 per QALY.

The simplest analytic model to present is the "3×3" model, which can be represented as a 3×3 square in which the 3 cost columns contain the costs of minimal, average and max therapy cost, and the 3 effect rows show the effect of minimal, average and maximal therapy effects. Costs are generally over the payer’s short-run relevant range, usually 1 year, and benefits are usually expressed in QALY’s over some broad time horizon. Benefits are generally converted to life years, which are then converted to quality-adjusted life years by multiplying life years by utility, which

is an overall measure of health status, from perfect health with a utility of 1 to dead with a utility of 0.

To incorporate non-fatal events, which can be devastating, they are converted to fatal events by estimating years of life lost due to non-fatal events (S. Weintraub & H. Lee, 2018). That is, it is assumed that acquisition of the condition by an individual with 75 years of life remaining and treatment yielding a life expectancy of 9 years would be assessed the same, whether or not QOL in the 9 years before death is considered. For the typical bivalirudin study with 1800 patients followed for 60 days and a cure adjustable life expectancy of 22 months, it is assumed that 86% complied with bivalirudin treatment at an average daily cost of $757.

1.9 8. Challenges in Biopharmaceutical Development

In a world with a rising and aging population and undesirable lifestyles leading to increasing chronic illnesses, the advent of breakthrough gene therapies could herald the dawn of a golden age in biopharmaceutical development. It is also the dawn of hope for those affected by diseases such as cancer and sickle cell disease. However, in conjunction with this hope, there are concerns on the horizon. The industry has a history of economic difficulties, having been forced to grapple with an exploding cost base, a series of bankruptcies and exits from the industry, and the collapse of companies that have been created as successors to former incumbents. Furthermore, there is competition from biosimilars, with big generics entering a growing market. Accusations of unfair pricing may not have affected the same extent reforms in health provision. All of this suggests that the future may be turbulent for biopharmaceuticals.

Biopharmaceuticals are medications produced using biotechnology involving recombinant DNA technology. This industry develops processes for producing biopharmaceuticals from recombinant base products and provides on-site construction and integration of biopharmaceutical manufacturing facilities. Sustainability principles can be applied to the biopharmaceutical industry to understand the overall impact of biopharmaceuticals manufacturing on the economy, society, and environment. The biopharmaceutical industry has evolved from traditional batch processes producing low-potent products in large stainless-steel bioreactor operated as a base-case for years, to current practices involving fully continuous manufacturing processes utilizing single-use technologies to produce multiple high-potency treatments in flexible manufacturing facilities.

8.1. Technical Challenges

As the biopharmaceutical industry matures, more attention is directed to the factors that will likely drive future technical challenges in the sector. Hence, an analysis demonstrating what is likely to change in the industry and how the scientific and engineering community can be a part of it is addressed here (Lalor et al., 2019). Highlighting information from the analysis stages of a project lead to identification of desirable outcomes. The biopharmaceutical industry is moving forward with greater availability of lower cost and higher quality biopharmaceuticals for a plethora of diseases and ailments. This promises a reduction in healthcare costs via better outcomes from prevention and treatment of disease. The economic viability of the biopharmaceutical industry and the continuing evolution of large bio-therapeutics demand performance in the areas of process development engineering, process control engineering, product restrictions on mass and tolerance for other components, and addressing the rapid emergence of parallel biomanufacturing lines (Korsmeyer, 2016).

Analysis of the technical challenges in biopharmaceuticals should consider what is likely to change in the industry within the next decade or so as the sector matures, the different factors that drive these changes and how these considerations shape the scope of the challenge. In this assessment, focus is directed on the production of biopharmaceuticals since bioprocess engineering already represents a well-defined field and there are tangible gaps in knowledge that should be addressed. The intent is to provide a useful frame within which to delineate biopharmaceutical production challenges worthy of research. It should be stated that not all elements of the checklists cited here will carry equal weight: the aim is to pose a broad ranging and careful analysis rather than to deliver an exhaustive list of all possible issues.

8.2. Regulatory Hurdles

Biopharmaceuticals exhibit an array of advantages over traditional medicines. They have a distinct composition, consisting of essentially one sequence but with different modifications due to their heterogeneity. Also, although they are produced through a series of well-defined steps, every modification makes them novel substances and necessitates comprehensive and continuous testing throughout production (Schellekens, 2009). They are more challenging to manufacture than traditional medicines requirements because they need a very controlled environment that can remain sterile, keep temperature at 37 °C, manage pH values, etc. These factors are very critical, and a sudden change in any of them can completely inactivate the biopharmaceutical product. Biopharmaceuticals also require continuous elaboration of comparability lists. However, they do not have a small peptide area as a limit of patent, unlike traditional drugs. Hence, on one side of the barrier, biopharmaceuticals are a very dynamic and promising area. On the other side, they create a very ambitious but complicated necessity for biosimilars.

Not only do biosimilar products have to fully adopt demanding requirements in testing but also, it has to be taken into account that these requirements vary from country to country, agency to agency, and product to product (Papas, 2015). These variations exist on account of diverse criteria used by evaluating agencies or scientific societies or guidelines supplied by the patent owner companies or scientific societies. Consequently, the presence of a very comparatively small number of biosimilars on account of the very high demand for biopharmaceuticals and biosimilars brings potential opportunities. Assessing all evident experiences of the past thirty years also in detail is a prerequisite for confronting the path shortages of biosimilar products, aiming not to miss any opportunity and focusing on enhancing assessment strategies.

8.3. Market Access Issues

Compatibility for biosimilars is an important property for physicians and regulators, enabling them to anticipate the likely clinical outcomes of switching. As with small molecules, there has been a general call to consider the regulation, testing and presentation of biosimilar products to assist with interchangeability. In the USA, the Medicines-user Interface (MUI) Safety Subcommittee of the Pharmaceutical Science and Clinical Pharmacology Advisory Committee recommends that the brand name should clearly differentiate the product from any reference biological. Two interrelated issues are raised with respect to the nomenclature of biosimilars; first, whether all biologicals should be given unique distinguishing identifiers; and second, whether a common faithful branding strategy should be adopted for biosimilars (Moorkens et al., 2016).

A lack of agreement on adverse-event reporting systems has made it impossible to follow patients who are switched to a biosimilar safely. The Public Health and Commercialisation of Biologics Act mandated the collection and identification of adverse events by product name. A physician in ASCOT engaged patients to consider how names of biosimilars could be identified safely: exaggerated naming strategies would confuse consumers, while a common name entailed an important shift in philosophy in how product information is conveyed to the public. The latter proposition would need regulatory reform, and considerable education to avoid confusing patients. One potential solution is to imagine biosimilars as an entirely new class of products, with a convention that companies provide information on population-wide studies of identified shared sequences, along with an explicit notation of quality assurance for any variations. The literature is fertile, dating back to before the first biosimilars entered the market. And yet notions of how physician beliefs, habits, quality, coverage, financing and ethics have been debated.

1.10 9. Future Directions in Biopharmaceuticals

Before entering the biopharmaceuticals and biotherapeutics sign of the future, there are coming technological changes in eighteen different areas which are going to offer new processes, new devices and new techniques. These advancements are addressed as: 1. Exploitation of space – the improved understanding of infectious disease processes is beginning to see some practical benefits, assessments of vaccine efficacy and scope exploration to treat cancer, 2. Exploitation of time – as an aspect of living, the more scientists are learning about the cellular biochemical pathways regulating physiological change, the more new approaches are emerging, 3. Photonics – sensors based on electrochemical or fluorescent principles, new approaches in microscopic analysis, screening and diagnostic assays, environmental monitoring and in vivo imaging, 4. Innovation computing – includes new materials/chemistries in inkjet printing applications and new deliver abilities, devices/publishing approaches/storage principles in data handling, model refocusing/new purposes in clinical/planning applications, 5. Combinatorial Micro-Biosystems – such micro-devices with multiple elements able to process parallel systems provide ubiquitous access to chemical processes and new analytical approaches, 6. Nanotechnology/nanoscale applications – safer biopharmaceuticals delivering elegance to micro-devices by functionalization of nanotechnology which is an opportunity across sciences disciplines, 7. Industrial flux – unit operations are being continued to be developed, 8. Knowledge management – the available information on chemical/biophysical sciences has never been more intense, 9. Space exploration – latest robotics, nanotechnology, bioactivity modeling, complex modification/analytical/in silico discovery/adaptive learning is on the verge of finding extant life on Mars/Moons, 10. T - Cells – historically/biologically important; each human produced T - cells; NTs in microbes rooted/synaptic/pruning & duration with secreted factors can now be studied and modulated with great promise, 11. Gene delivery – safe delivery of any gene anywhere in any organism indefinitely is done by microbubbles, 12. Energy capture/storage distribution – new synthetic methods producing low cost semiconductors achieving luminous quantum yields/photo conversion efficiencies, 13. Dynamic embryos – developmental biology entered a quantum leap, 14. Quantative in vivo drug activity mapping – escalation in drug efficiency during preclinical development at nanomolar concentration range has remarkable industrial implication, 15. Quantum computation – epigenetics/pharmacogenomics/systems biology will be rewritten with this new paradigm with unprecedented computing capacities, 16. Intel inside – predictive/synthetic genes/circuits with arbitrary desires/functionalities will be assembled with new combinatorial

devices, 17. Massive connectivity – unprecedented parallelism dimensioning selection accesses/reinforcement mechanisms enabling a spontaneous group cognition, 18. Broad perspectives in metabolism – health issues are targeted after restoration of patterns first learned to eliminate time frames/change with aspirations/complexity in years time span outside of the human brain.

9.1. Personalized Medicine

N-of-1 medicine refers to empirical experiments undertaken in an individual patient, often by personal means, that inform clinical diagnosis and therapy (Wang et al., 2024). N-of-1 medicine is an alternative to evidence-based medicine which conventionally matches treatments to groups of patients defined by disease. This practice is "stubbornly inefficient", a consequence of variation in individuals' biology and living in diverse environments. To explicitly center patients' data requires digital medicine, the emergence of which is planetary. Global malaise from the COVID-19 pandemic accelerated this emergence by digital pathology, and even more so, on the patient side via remote medical consults, at-home kit testing, wearables and implantables. Regular collection and remote viewing of data from these devices yield a patient's many digital fingerprints, immortalized in cloud storage. Experimental interpretation produce digital twins, wherein their bodies, organ systems and biochemical networks are simulated by digital models from the data. N-of-1 medicine refers to the practice of performing patient-empirical experiments using ever-increasing digital twins, wherein the physicians' or care givers' therapeutic hypotheses have been converted to actionable tasks for the digital twin. The digital twin can immediately, optionally involving vast computing resources, compute patient-specific therapeutic regimens from the knowledge of the cellular responses of on-target drugs, drug-bioengineered compounds and lifestyle modifications. Remedies are suggested to return to the baseline, or intervene at the earliest polynomial time, as befits N-out-of-1 remedy selection.

3D printing technology allows easily build various complex structures at the microscale. The precise control in fabrication methods and a large variety of available materials supported by this technique allow various biomedical applications such as drug manufacturing, tissue engineering scaffolds, biosensor and many more (Marcia Vaz & Kumar, 2021). 3D printed scaffolds with desired sizes, shapes and porosity were manufactured to foster tissue regeneration in vivo. Pharmaceutical companies have also studied 3D printing as an alternative technology for drug manufacturing and coating. FDA has already approved 3D printed tablets, so drug delivery devices with designed release patterns and sizes can be produced easily and cost of the drugs also reduced. Bioprinting, as a special application of 3D printing, is also regarded as the future of medicine, meanwhile bioink and post bioprinting treatments are critical factors in bioprinting quality and take longer time to improve. To meet the demand for personalized medicine, 3D printing technologies would hope to open up new possibilities in this field in the future.

9.2. Innovative Drug Delivery Systems

Drug delivery systems are crucial in addressing the issues surrounding biopharmaceuticals and surrounding natural compounds that have the potential to be developed as medicines. Small molecules can be targeted using a range of techniques developed for solid organized structures. Natural products and biotherapeutics overcome many issues taken into account when considering drug delivery systems for small molecules. These often adopt a secondary or tertiary structure,

which enables targeting without a nanocarrier. Technologies have emerged to produce biotherapeutics using simple proteins or peptides that can be delivered as monomeric compounds. Nevertheless, these advancements often come alongside issues of biophysical instability, leading to aggregation and precipitation. A breath-taking number of studies using template methods have been published recently that deliver natural products and biotherapeutics effectively pre-empting the aforementioned issues (A. Obeid et al., 2017). It is generally accepted that active drug compounds do not act whether it be natural or synthetic in a bioactive state, in a free solution. The drug needs to be bound to a carrier (nanocarrier) that can modulate the nature of the drug and the biological pathways. The first drug delivery systems like liposomes were described in 1970 where phospholipids and cholesterol lysed in organic solvents can be extruded through membranes to generate liposomes capable of encapsulating drug-loads many hundred times greater than its weight. Around this and the previous decades, the recognition that chemicals and biotherapeutic products can have multiple therapeutic roles is areas to explore in the search for improvement of drug delivery systems. All active drug compounds first need to present bioavailability before they can interact with target proteins, enzymes or genes. The knowledge of what it takes to reach the site of action by the drug is crucial before a product can be designed. A fundamental understanding that what dictates resolution and release of a drug from a nanoscale carrier in interplay with various characteristics of the bio-environment is essential on scale-up manufacture of formulations (Grenha, 2012). Therefore, naturally derived biopharmaceuticals are ideal candidates for drug delivery systems since they can target small organized substances in organisms without the need for an extra carrier and stabilizing agents are cost compatible with formulation. Plant-whole extracts, fractions, and subsequently purified compounds of these deliver biologics to injection paths with a pharmacological strength that controls or prevents disease-like conditions. Transparently, such biotherapeutics do not bind by covalent bonds, but through weaker interactions. A plethora of disciplines has risen to understand how these natural products act in biological systems for biotechnology to market needs, while still opened to on-budget molecule-ing testing detrimental for developing low-water soluble drugs.

9.3. Emerging Technologies

Understanding the human genome and its associated proteome is the principal goal of genomics and proteomics, respectively. Planning and methods have already been established to survey a large portion of human protein-encoding genes. Microarrays that have complementarity to a broad portion of the human genome are facilitating systematic studies of genomics/proteomics expression and polymorphisms. These technologies have the power to elucidate the majority of key interactions, or inter-actomes, involving proteins and DNA and to provide a deeper understanding of the chemistry of neighboring modules (D. Sindelar, 2013). The functional annotation of the human genome will rapidly enrich the existing repositories of biomolecular databases with landscape-scale human genetic variation data and disease association information. Such information should enable a fresh wave of realization and exploitation of molecular medicine. Meanwhile, innovative technologies and analytical tools need to be developed to enable efficient large-scale management, organization, and mining of this burgeoning biomedical knowledge. The genome is considered the primary level of life, having an informational role in biological systems. However, as the central dogma strictly states, genetic information is not independently sufficient for gene expression and phenotype inheritance; gene products (RNA, proteins) also play direct roles in these aspects and have to be functionally regarded as primary

carriers of genotype and phenotype. As a further consequence of the central dogma, epigenetic interactions, errors, or modifications of DNA add another layer of profound complexity to genetics. The genome and its associated proteome represent an intrinsic blueprint that imposes constraints on cell variation and a stable reference for cellular evolution. Recent advances in high-throughput technologies have provided unprecedented experimental evidence and comprehensive knowledge on the static aspects of genomics and proteomics as discrete molecular networks. A bias towards one-dimensional mutual information appears to be imprinted on given genes or proteins as if they were atomic structures. Consequently, probabilistic modeling based solely on static networks fails to account for the kinetic aspects of similar forms of interactions and their evolutionary incorporation of more complex processes. It is hypothesized that protein-coding genes represented with a series of coupled parameters should work as dynamic regulators of the complementary DNA between highly conserved and variable regions in the evolution of complex cellular patterns and systems.

1.11 **10. Ethical Considerations**

Is it ethically permissible to conduct clinical research with children, considering their vulnerability? Should adults with diminished capacity be enrolled in clinical trials? These questions often raise concerns regarding the ethics of clinical research in general but are usually only pursued as such. Bioethics discussions commonly focus on one particular aspect of the biopharmaceutical enterprise, such as clinical research, while ignoring the upstream and downstream components. They seldom consider the whole biopharmaceutical enterprise, the biomedical bioethics norms applicable to it, and how they should be applied from a bioethics standpoint (E. Van Campen et al., 2021). A broad definition of the biopharmaceutical enterprise or industry is considered. The applicability of biomedical bioethics norms to it is explored, as is the application of those norms, at company and case-specific levels. Such questions should be addressed at a company guidance level, thereby providing direction to the company. This is referred to as a first-order bioethical consideration. The need for a company definition of the biopharmaceutical enterprise is demonstrated. The phrase “biopharmaceutical healthcare products” is explained. It is argued that the scope of this definition should include any healthcare product that is a medicine, vaccine or diagnostic and that has been developed, manufactured or marketed by the company.

As part of the compendium of values and principles that comprise the healthcare product business segment, company values and principles play an important role for establishing standard operating procedures to protect the interests, rights and well-being of research participants and patients in the biopharmaceutical enterprise. Based on this bioethical understanding, application of bioethics norms should be undertaken at two levels. The first is at a company guidance level, including such considerations as definitions, protocols, values and principles. In other words, the question here is what the biopharmaceutical enterprise or industry is (upstream). The second is at a case-specific level, such as a clinical development team’s decision on clinical trial design, at which microbioethics norms apply (downstream). Here, the focus is solely on the first level.

10.1. Access to Medicines

Inequitable access to essential medicines in developing countries (DCs) could be a potentially culpable factor for the disastrous outcomes and acceleration of the global epidemic. At national

and international levels, frameworks for improved access to medicines must be developed and implemented if any desired and doable outcome is expected. Nations, international entities, pharmaceutical firms, and other stakeholders all have complementary and subdividing responsibilities in combating biomedical and pharmacoepidemics. There is a hierarchy among agents involved in increased access, but concerning the mentioned devises and their application to expeditiously increase access to medicines, accountability should rest mainly with nations and international entities, while significant accountability also lies with pharmaceutical companies and other stakeholders (Ahmadiani & Nikfar, 2016).

Subregionally, cooperation of health authorities, deep stakeholders, and all other agents who can increase access to medicines should be established. Competitively pro-competitive regional access-promoting monitoring frameworks and reporting mechanisms to prevent anti-competitive acts and behaviors, and binding stakeholder-specific acts to impose damages and punishments for violations should be discussed. Minimally, established subregionally sustainable living community investments should be achieved, and countries with impediments should be given sanctions. Additionally, models of pharmaceutical firm accountability and auditing procedures enhancing fast delivery of compliance and redress to rights must be developed and implemented (Stevens & Huys, 2017).

At the community level, tethered participatory local monitoring frameworks should be developed and appropriately empowered, and in this context, the Public Wishness-Sustained Access to Pharmaceutical Medicines Act should be passed, enacted, and enforced. This act must comprehensively elaborate on the responsibilities of DC health authorities, pharmaceutical firms, global health organizations, and increasing access stakeholders. Increased upon sound understanding of human mortality, biomedical and pharmacoepidemics, complexities and inequalities in access to medicines, stakeholders, and mechanisms involved, this requirement can be minimized to a less utopian concern. It is hoped that with the aforementioned accountability, which is presently a new but unheeded concern, delayed goals for increased health, wellbeing, familyism, sustainability, and decreased inequity and mortality would be achievable.

10.2. Patient Consent

The ethical principle of consent is imperative for various biomedical research and clinical applications. Yet less is known about patient understanding of the external sharing of personal health information (PHI) outside direct care relationships. This study determined the consent preferences of patients at an academic health care institution regarding external PHI sharing for non-care purposes (Tosoni et al., 2021).

Recent years have seen rapid technological advancements in health care and research. These innovations are leading to an ever-growing volume of health information about individuals that can be stored, repurposed, and monetized. At the same time, limited individual oversight of and control over this health data is available. Lay understandings and perceptions of personal health privacy and data governance are culturally situated, and reflect various underlying and often conflicting values (including notions of ontological and epistemic ownership). A belief that researchers, as a professional class, ought to safeguard the trust that governs the patient-researcher relationship begs examination in the context of a much broader, industry- and sectoral-wide community of health data stakeholders.

Two main scenarios were applied to identify consent preferences regarding the external sharing of PHI: care-related external sharing and non-care-related external sharing. For care-related external sharing, raters were unambiguously positive, eliciting an expectation of continued evidence-based patient care. Conversely, for non-care-related external sharing, raters were generally negative, voicing concerns over erosion of patient privacy, loss of control, exploitation of health data for profit, and inability to opt-out if subsequently affected. The expressions of consent preferences fell along a theoretical continuum of de-identification, generalization, pooling, intent-based sharing, and full-identification. Justifications bordering de-identification, even when contradictory, tended to focus on upholding patient autonomy and privacy, alleviating concern over amassment of sensitive data.

Most patients (55%) indicated a preference to be asked permission before their PHI is shared outside the circle of care. There was a consistent desire for greater transparency and autonomy, particularly revealing a generational shift wherein younger patients preferred more informed consent options. Recommendations include opt-in approaches to seek permission for research contact and the provision of genuine opportunities for uncertain patients to consider their consent decisions and revisit them later.

10.3. Biotechnology Ethics

The biopharmaceutical enterprise is at the intersection of life sciences, clinical research, clinical care, public health, and business. This asymmetrical intersection presents unique operational as well as ethical challenges. Ethical integrity in research, development, manufacturing/supply, marketing/sales, and complaint handling is foundational to the recovery of safe and effective medicines. Ethical integrity in clinical care, public health, business development, and market access is essential to the appropriate use of biopharmaceuticals once delivered to the marketplace. Yet ethical integrity is an aspirational state of being, never fully reachable, and rigorous ethics norms and standards should be applied and complied with to achieve as close to that state as is reasonable (E. Van Campen et al., 2021).

As with other participants in health care and health policy, the biopharmaceutical enterprise frequently faces issues with important ethical implications. Biopharmaceutical companies, however, confront certain ethics issues that may escape the attention of policy makers or regulators or will not be fully addressed via public policy or industry guidelines. A few examples of topics related to biopharmaceutical as well as public health ethics include: access to medicines; shortage of critical medicines during a worldwide pandemic; use of human biological samples from patients for research, commercial, or other purposes; quality of life measures for novel cancer and regenerative medicines; diversity and inclusion in clinical trials; conduct of clinical trials for novel COVID-19 vaccines during a worldwide pandemic.

These topics either uniquely confront the biopharmaceutical enterprise or confront it in ways not faced by other health professional or health system participants. Neither public policy nor pre-existing industry guidelines are sufficiently prescriptive on these topics, requiring systematic consideration of bioethics standards, application to individual company settings, and development of guidelines. Bioethics is an interdisciplinary field concerned with ethically significant issues that arise in health care, medicine, and the life sciences. Bioethics directly or indirectly concerns any institution with a research, clinical care, or public health mission that generates unmet medical

need(s). The application and specification of bioethics norms for context- or setting-specific use differ by the mission and characteristics of the institution.

1.12 11. Conclusion

Biopharmaceuticals are a class of products derived from biological sources. In this context, the term “biopharmaceutical” is used to refer to therapeutics engineered using biological systems, as well as other biologically-derived products such as vaccines. Biopharmaceuticals are a diverse group of products. Therapeutics in the biopharmaceuticals industry are frequently categorised based on the type of pharmaceutical compound comprising the product. The biopharmaceuticals industry has developed from the large-scale manufacture of blood-derived therapeutic proteins to the modern generation of complex products that include monoclonal antibodies, cell and gene therapies, and biosimilars. Biologics are large, complex molecules compared to traditional small molecule drugs. As a result, biopharmaceuticals are difficult to manufacture, highly expensive, and challenging to analyse. The results of a study show that while the overall Indian pharmaceuticals market at approximately $17 billion is growing at an annual rate of over 12%, the biopharmaceuticals segment holds an even larger potential, currently valued at $2 billion (Lalor et al., 2019). With a compound annual growth rate of 24%, the biopharmaceuticals market is expected to reach nearly $7 billion by 2020. The biopharmaceuticals segment is dominated largely by the monoclonal antibody based therapeutic and diagnostic segments, which accounted for 85% plus of the market share in FY 2015. The Indian biopharmaceuticals sector, at approximately $1.4 billion, is mainly split between biologics and biosimilars at 66%, and diagnostics at 34% in FY 2014. It is expected that this split will change in favour of biologics and biosimilars, which is expected to reach over 90% of the forecasted biopharmaceuticals revenue of $3.9 billion in FY 2018. The Indian biopharmaceuticals market is led largely by biosimilars. The first generation monoclonal antibody biosimilars gave India an opportunity to develop technical competencies and early entry advantages that helped secure larger US market shares for the various Indian players in the global space. Newer entrants are focusing on the emerging biosimilars, especially for the fusions and complex glycoproteins that are harder to dissect and recombinantly develop.

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