1

Introduction to Biomanufacturing

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Abstract
The process of creating economically significant biomaterials and biomolecules using biological systems, such as cells, enzymes, or organisms, is known as biomanufacturing. Pharmaceuticals, food and beverage, chemicals, and biofuels are among the businesses that employ these materials. The process for creating solid and porous biomedical implants was thoroughly studied to ensure their effective use. Technologies such as electrospinning, additive manufacturing, and powder metallurgy have been identified as promising approaches for creating porous, mechanically adjustable ceramic and metallic implants for use in medicine. The chapter discusses the transformations in biomanufacturing, fundamentals of bioprocessing, and biomanufacturing, innovations in bioprocessing, need of bio-based economy, biological systems, progress in biomanufacturing, case studies of bioprocesses, overview of biomaterials, manufacturing process for porous implants, investment and strategic alliances to boost commercial biomanufacturing, challenges and limitations in bioprocessing and biomanufacturing, and future prospects of biomanufacturing.

***Keywords*:** Biomanufacturing, biomaterials, implants, biological systems, bioprocessing, biofactory

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1.1 Introduction

Since its origin, biomanufacturing, the technique of harnessing live organisms to create useful products has advanced significantly. Biomanufacturing is the process of producing commercial goods for food, energy, material, pharmaceutical, and agricultural industries using biological systems such as enzymes, bacteria, cells, tissues, plants, and animals [1]. Technological developments, scientific breakthroughs, and a growing understanding of biological systems have made it possible to optimize biomanufacturing procedures and produce new applications throughout time. In the earlier days, the food and beverages were prepared using microbes like yeast and bacteria. For example, the yeast is utilized in the fermenting process to ferment sugars and generate alcohol. Similar to this, bacteria are applied in the making of cheese and yogurt; it is used to transform milk into their respective products.

By the development of genetically modified organisms and capable of producing particular proteins or other chemicals, the application of recombinant DNA technology in the 1970s and 1980s transformed biomanufacturing. The first recombinant protein, human insulin was invented in the early 1980s to treat diabetes on an industrial scale. The biomanufacturing technology continued to advance throughout the 1990s and 2000s. Advances in directed evolution and the rapid screening of hundreds of potential drug candidates were made possible by high-throughput screening techniques. The protein engineering made it possible to boost biomanufacturing methods and produce new enzymes and other proteins with particular roles. Biomanufacturing is now a significant part of the biotechnology and pharmaceutical sectors. Biomanufacturing techniques are exploited to generate many of the vaccines and medications required to prevent and treat diseases, and new uses for biomanufacturing are frequently being explored. The application of synthetic biology, which involves creating new biological systems with particular roles, is another rapidly developing the field of biomanufacturing. The biomanufactured new organisms can perform the specified tasks, including removing ecological pollutants; this technology has capability to completely transform biomanufacturing.

The most significant biomanufactured products and their applications are discussed:

- Insulin: Blood sugar levels are regulated by biomanufactured insulin to those with diabetes.

- Vaccinations: The production of vaccinations, such as the COVID-19, HPV, and flu vaccines, is done using biomanufacturing.
- Enzymes: Biomanufacturing creates enzymes that are utilized in several industrial processes, including food processing, laundry detergents, and biofuels.
- Antibodies: Monoclonal antibodies are produced *via* biomanufacturing and are utilized to cure many diseases, including autoimmune disorders and cancer.
- Biofuels: Biofuels such as ethanol and biodiesel are produced through the process of biomanufacturing.
- Hormones: Hormones including growth hormone, erythropoietin, and follicle-stimulating hormone are generated through biomanufacturing.
- Industrial chemicals: Biomanufacturing is the process used to create industrial chemicals, including solvents, bio-based chemicals, and biodegradable plastics.
- Amino Acids: Amino acids used in food additives and animal feed are produced through biomanufacturing.
- Nutraceuticals: Vitamins, probiotics, and prebiotics are examples of nutraceuticals that are made using biomanufacturing.
- Personal care products: Products including lotions, creams, and shampoos are made by biomanufacturing.
- Food: Dairy items, fermented edibles, and various foods are produced using microorganisms.
- Bio-based fibers: Environmentally sustainable alternatives are used to synthetic fibers in clothing and other industries.
- Biopesticides: Products for pest management made from natural sources are called biopesticides.
- Biofertilizers: Additives to soil that support the health and growth of plants.

Biomanufacturing encompasses metal biorefineries, regenerative medicine, and a range of chemical products [2, 3, 25]. These products may be reformed through different methods, including recombinant DNA technologies, synthetic biology and protein and metabolic engineering, or they may be applied in their unaltered form [4].

Latest studies explore the rapid demand of bone and joint replacements. According to estimates, most people over 45 years with bone weakness, inflammation of the joints, and cartilage deterioration, which leads to bone degradation under conditions of constant cyclic loading [5, 6]. This is the primary reason for bone joint loss due to the friction and deterioration of the physical and mechanical characteristics of normal human bone. The best solution to these issues is total joint replacement (TJR), in which artificial implants are used to replace load-bearing joints [7, 8]. Artificial implants are made of biomaterials and consist of all or a portion of a live structure that substitutes a natural function to enhance the quality of the human body. Three elements determine how stable implants are: (i) the mechanical, chemical, and morphological characteristics of biomaterials; (ii) their biocompatibility; and (iii) their nontoxicity [9, 10]. The reactions of implanted biomaterials indicate that titanium alloy, magnesium-based alloys, and stainless steel are the main prevalent metallic biomaterials. It is important to note that the stiffness values of SS, Co, and Ti alloys are significantly higher than those of cortical bone. They should have respectable chemical and mechanical qualities. Foreign body reaction, acute and chronic inflammation, and blood–material interaction are examples of host reactions that typically happen in the biomaterial implantation. A wide range of implant biomaterials close to the implant site can cause different kinds of reactions.

The changes in biomanufacturing, bioprocessing fundamentals, biomanufacturing innovations, the need for a bio-based economy, biological systems, biomanufacturing progress, case studies of bioprocesses, biomaterials overview, the manufacturing process for porous implants, investment and strategic alliances to increase commercial biomanufacturing, bioprocessing and biomanufacturing challenges and limitations, and biomanufacturing's future prospects are all covered in this chapter.

1.2 Transformations in Biomanufacturing

The technological advancements that paved the way for biomanufacturing usually occurred concurrently and led to new revolutions. Revolutions in biomanufacturing are explained as follows [11]:

(i) Premodern Biomanufacturing

Biomanufacturing was certainly used to transform one sort of food into another thousands of years ago, before people were aware of fermentation. According to documents dating back over 9,000 years, the ancient Chinese may have made wine with rice, honey, and fruits as raw ingredients. Comparable accounts have been found in other texts that detail the Sumerian and Babylonian brewing of beer around 6000 BC [12], as well as the baking of bread in Egypt. Prior to

Louis Pasteur popularizing fermentation, it was employed in several processes, including pickling food and making cheese, curd, beverages, and culinary sauces. These fermentation methods could be categorized as premodern biomanufacturing methods since they employed naturally existing, readily cultivable mixed microorganisms that could create desired products from simple feedstocks and included solid state fermentation.

(ii) Biomanufacturing 1.0

The production of primary metabolites is the main focus of the bio-manufacturing 1.0 revolution. Biomanufacturing 1.0 may have begun in the 1910s when Chaim Weizmann identified Clostridium acetobutylicum and established the fermentation processes for ethanol, butanol, and acetone. Pure microbial cultures were used in an anaerobic liquid fermentation system for the first time in biomanufacturing 1.0. The demands of the market acted a significant role in the progress of fermentation technology. The major goal of biomanufacturing 1.0 was to produce primary metabolites. The most fundamental metabolic byproducts are needed for normal growth and reproduction. Acetone, n-butanol, glycerol, nucleosides, carbohydrates, organic acids, amino acids, and so forth are examples of these. Similarly, to meet market demand and reduce production costs, the leading glutamate producers shifted from chemical synthesis to microbial fermentation for the commercial production of monosodium glutamate [13]. The amino acid that is most widely synthesized, is monosodium glutamate.

(iii) Biomanufacturing 2.0

The primary focus of this biomanufacturing revolution was the generation of secondary metabolites, which began during World War II with the fermentation of penicillin, tetracycline, and streptomycin. Unlike primary metabolites, which are produced by a limited number of species within a taxonomic group, secondary metabolites are not required for an organism's growth, development, or reproduction. However, being a crucial component of natural defense, they provide a selection advantage to the producing organism, enhancing its chances of survival. These secondary metabolites are commercially useful to humans and are used as components in medications, flavors, fragrances, and colorings. Biomanufacturing 2.0 built upon the previous revolution in terms of the employment of specialized mutant microbial strains and aerobic submerged fermentation techniques.

(iv) Biomanufacturing 3.0

The transition in the 1980s from the synthesis of primary or secondary metabolites to large proteins crucial for catalysis and medicine led to the creation of Biomanufacturing 3.0. The two main technologies that this revolution concentrated on were improved cell cultures and recombinant DNA technology. After Stanley Cohen and Herbert Boyer created the first *in vitro* recombinant DNA plasmid in 1973, other for-profit initiatives using the same technology began to appear. These businesses concentrated on high-value pharmaceutical proteins since they are difficult to extract from their natural sources and costly to synthesize. Biomanufacturing 3.0 made rapid progress with the sequential production of recombinant proteins such as growth hormone and human insulin. During this time, customized mammalian cell cultures were used to produce human erythropoietin, a protein hormone that increases the rate of RBC synthesis, in a low-cost with higher-quality manner. Additionally, the research of antibody-drug conjugates for the treatment of cancer gained momentum [14]. Furthermore, a crucial element of biomanufacturing 3.0 was the creation of recombinant enzymes for commercial and scientific applications. New England Biolabs was the first company to be established in 1974 for the commercial production of enzymes needed for recombinant DNA technology, such as restriction enzymes and DNA polymerases. The main challenges of this production encountered the limited use and poor stability of enzymes were overcome during the 1980s to 1990s, which included immobilization of enzymes [15, 16]. Later, in the 1980s, a few more companies were founded, including Novozymes and Genencor, which used technology for structure-based protein engineering and focused on the mass production of enzymes used in food, chemical, detergent, and textile industries. The third and current wave of enzymes focused on creating the customized enzymes with major chemical changes starting in the middle and late 1990s [17, 18].

(v) Biomanufacturing 4.0

The production of biology-driven organisms, *in-vitro* bio-systems for artificial starch synthesis, metabolic engineering for iso-butanol production, and human tissues are the focus of a different category known as biomanufacturing 4.0. The world's most urgent issues, including those pertaining to food safety, energy generation, water supply, and sustainability, may be resolved by the bio-manufacturing 4.0 revolution. Additionally, in the biomanufacturing industry, implementing digital technology and artificial intelligence has become essential and a competitive advantage. Consequently, many biological product manufacturing firms today depend on more robots than humans. The complete implementation and execution of robotics is yet a ways off [19]. In recent years, the biomanufacturing industry has grown more and more dependent on the advancement of Internet of Things (IoT) technologies. The concepts of a data-driven, networked society have replaced those of industry. Industry 4.0 encompasses the biomanufacturing industry, which is characterized by the application of cyber-physical-based systems. The massive revolution brought about by Industry 4.0—which is fueled by big data, cloud computing, and digital transformation—has altered our daily lives. The current biomanufacturing revolution, referred to as "Biomanufacturing 4.0," is focused on producing a broad range of novel, sustainable, effective, and safe products associated with pharmaceuticals, regenerative medicine, renewable energy sources, artificial food, and the integration of various biological tools from synthetic biology to metabolic engineering, among other things [20].

(vi) Biomanufacturing 5.0

Biomanufacturing 5.0 signifies the latest development in production powered by biotechnology, incorporating cutting-edge technologies such as artificial intelligence, machine learning, robotics, and the Internet of Things (IoT) to improve accuracy, efficiency, and sustainability. In contrast to previous generations, biomanufacturing 5.0 focuses on real-time data analysis, digital twins, and intelligent automation to enhance each phase of the production process, from cell culture to product purification. This method not only speeds up innovation but also promotes personalized medicine and eco-friendly manufacturing practices. Among other fascinating advancements in chemical synthesis and assembly that are employed to biological processes, components, and systems, synthetic biology may now modify already-existing biological cells, produce synthetic cells, transplant synthetic genomes, and produce chemical models. Self-regulating biological self-organization and self-production processes are successfully added by synthetic biology, and these systems are of interest to artificial intelligence [21].

1.3 Industrial Biotechnology and Biomanufacturing from a Historical Perspective

Industrial biotechnology has its origins in ancient civilizations, when bread, beer, and wine were produced using early biotechnological techniques like fermentation. The foundation for contemporary biotechnological applications was established by these procedures, which were conducted without a scientific understanding of the microorganisms involved. A scientific foundation for comprehending and working with microbes was established by the 19th-century development of microbiology, which was led by trailblazers such as Louis Pasteur and Robert Koch [22]. Significant developments during the 20th century accelerated the growth of industrial biotechnology. The pharmaceutical industry underwent a sea change in 1928 when Alexander Fleming discovered penicillin, and it was mass produced during World War II. Large-scale fermentation methods were developed at this time, making it possible to generate vitamins, antibiotics, and organic acids [23]. The commercialization of genetic engineering initiated in 1976 with the founding of the first biotechnology companies, such as Genentech. Researchers invented the ability to alter the genetic material of organisms, leading to developments in recombinant DNA technology during the 1970s, which essentially changed the discipline. This method empowered the development of inherently modified microorganisms by generating human insulin, various therapeutic proteins and growth hormones. A significant milestone demonstrates the potentiality of biotechnology to generate complex biological molecules, which was the authorization of recombinant human insulin in 1982 [24].

The domain of industrial biotechnology started the quick growth during the late 20th and early 21st centuries. Developments in proteomics, genomics and systems biology accelerated more accurate genetic modifications, providing a deeper perception into cellular functions. The pace of innovation was further boosted by the initiation of high-throughput screening techniques and automation. During this period, synthetic biology developed, which implies the design and development of unique biological components and systems by integrating the concepts from biology and engineering [1]. One of the most substantial transformations is the growth of biomanufacturing, remarkably within the pharmaceutical industry. The biomanufacturers produce the biopharmaceuticals such as cellular therapies, monoclonal antibodies and vaccines utilizing living cells. These medicines are essential for recovering various diseases, including autoimmune disorders, cancer, and infectious diseases due to their intricate specificity and nature. As the field continues to grow, several key trends are forming its future. The addition of digital technologies such as machine learning (ML), Internet of Things (IoT), and artificial intelligence (AI) is changing biomanufacturing and bioprocessing. These technologies augment the product quality and productivity by facilitating optimization and real-time monitoring of manufacturing processes. Furthermore, advancements in synthetic biology and metabolic engineering are growing the range of products that can be progressed through biotechnological methods [25]. The chronological context of industrial biotechnology focuses the remarkable progress made over the past century. The advancements in engineering science and technology, the field has experienced the continuous evolution, from the early days of fermentation to the sophisticated biomanufacturing processes for present days. This progress has not only converted industries but has also contributed to addressing global challenges such as environmental sustainability, healthcare, and energy [26].

1.4 Fundamentals of Bioprocessing and Biomanufacturing

The main aspects of industrial biotechnology are biomanufacturing and bioprocessing, which develop the biological systems to produce goods with a market assessment. The production of biological materials, such as biochemicals, biofuels, and medicines can be optimized by a variety of technologies that fall under these categories. To fully utilize these methods, it is mandatory to realize their foundations [27]. Upstream processing is the first step among several crucial steps in bioprocessing. The preparation and growing of the microorganisms that will provide the intended product are involved in this step. The efficiency of the production process is decided by the choice of appropriate cell lines or microorganisms. To enhance these biological systems' productivity, genetic engineering techniques are commonly used [28]. The next step is fermentation in the bioprocessing process. The intended product is formed during fermentation by generating cells or microorganisms in bioreactors under carefully monitored conditions. The ideal growth conditions, such as pH, nutrition supply, temperature, oxygen levels, bioreactor design and operation are important. The scalability and efficiency of bioprocessing have been significantly augmented by the developments in bioreactor technology, such as the creation of continuous fermentation systems and single-use bioreactors [29].

The recovery and purification of the product from the fermentation broth create the downstream processing, which comes after fermentation. A number of procedures are involved at this stage, including purification, product isolation, and cell separation. To get the product's concentration and purity, the techniques like chromatography, filtering, centrifugation, and crystallization are commonly utilized. The product's nature and specifications for its intended use decide, which downstream processing techniques are applied [30]. By integrating bioprocessing into a unified production system, biomanufacturing promises the smooth transfer of information and materials from raw materials to final products. Upstream and downstream methods must be directed as part of this integration, and quality control techniques must be put in place to ensure the consistency and safety of the final product. Real-time monitoring and management of biomanufacturing methods have become simpler with the use of sophisticated control systems and process analytical technologies (PAT), increasing efficiency and decreasing adaptability [31]. The adoption of continuous manufacturing techniques is one of the major improvements in biomanufacturing. Continuous manufacturing functions in a steady-state mode, where raw materials are frequently fed into the system and products are constantly collected, in contrast to typical batch processing. The lower prices, shorter production times, and higher-quality products are just a few advantages of this strategy. The potentiality of continuous manufacturing to transform biomanufacturing has been exposed by its effective application in the production of biopharmaceuticals, including monoclonal antibodies and vaccines [32]. The creation of single-use technology, which makes the use of disposable bioreactor components, is another significant breakthrough. These technologies provide several advantages, such as decreased capital investment, a decreased danger of cross-contamination and greater flexibility. Particularly, single-use bioreactors have become more and more popular in the biopharmaceutical sector, where they are applied to produce therapeutic proteins and vaccines in tiny to medium-sized batches [33].

1.5 Innovations in Bioprocessing

The contemporary advancements in technology and an enhanced understanding of biological processes have resulted in significant innovations within the field of bioprocessing. These improvements have progressed the scalability, efficiency and sustainability of bioprocesses, thereby improving their applicability in industrial environments. Key areas of innovation consist of novel bioreactor designs, synthetic biology, the implementation of process analytical technologies (PAT) and advanced fermentation techniques.

(i) Advanced Methods of Fermentation

The core principle of bioprocessing is fermentation, which involves cultivating microorganisms or cells to manufacture the specific products. Recent developments in fermentation methods aim to enhance the productivity and yield through the optimization of various conditions. For example, the high-cell-density fermentation pointedly increases the product concentration by allowing the growth of numerous cells within a limited volume. This method is particularly beneficial in the production of biopharmaceuticals, where high yields are vital for economic feasibility.

Another important innovation is the growth of fed-batch and continuous fermentation methods. Fed-batch fermentation allows for extended production periods and increased cell densities by methodically introducing nutrients into the bioreactor. Conversely, the continuous fermentation keeps cells in a productive state for extended durations by perpetually supplying fresh medium while simultaneously eliminating spent medium and cells. In comparison to traditional batch fermentation, the continuous methods offer numerous advantages, including improved product uniformity, reduced downtime, and enhanced output.

(ii) Novel Bioreactor Designs

The productivity of bioprocessing is pointedly affected by the design and operation of bioreactors. Recent developments in bioreactor technology have focussed on oxygen transfer, improving mixing, and temperature regulation—all vital factors for product development and cellular growth. Due to their lower initial investment, adaptability, and reduced risk of cross-contamination, single-use bioreactors made from disposable plastic materials have become progressively popular. These bioreactors are mostly beneficial for processes that require stringent sterility and for production on a small to medium scale. Another important innovation is the use of perfusion bioreactors, where cells continue within the bioreactor while the medium is incessantly refreshed. This setup is ideal to produce biologics such as monoclonal antibodies and viral vectors, as it supports extended production durations and high cell densities. Additionally, the incorporation of sensors and advanced control systems in bioreactors enables adjustment of process parameters and real-time monitoring, thereby improving the productivity and product quality.

(iii) Metabolic Engineering and Synthetic Biology

Metabolic engineering and synthetic biology have transformed the bioprocessing by empowering the formation of unique cell lines and microbial strains tailored for specific industrial applications. Through genetic alterations, it is possible to enhance the metabolic pathways to progress the production of desired molecules, reduce byproduct formation, and improve cell growth and stability. For example, the modified yeast and bacteria create biofuels, bioplastics, and pharmaceuticals more skilfully than their wild-type counterparts. CRISPR-Cas9 technology acts as a controlling technology for precise genome editing, allowing for the targeted alteration of genes that perform a significant role in metabolic pathways. This technique has empowered the identification of novel biosynthetic pathways for valuable compounds and has improved the development of microbial strains with enhanced production capabilities. The integration of metabolic engineering and synthetic biology extends the range of organically formed products, ensuring that bioprocessing remains at the forefront of innovation.

(iv) Sustainable Bioprocessing
Sustainability performs a substantial role in modern bioprocessing with initiatives, focused on reducing ecological impact and augmenting the economic viability of biotechnological production. One of the developments in this area is the utilization of renewable feedstocks as substrates for microbial fermentation, including industrial byproducts and agricultural residues. This technique supports a circular economy by reducing the dependence on fossil fuels and enhancing the value of waste materials. Additionally, the progress of more effective and less energy-consuming separation and purification techniques has further boosted the sustainability of bioprocessing. For example, the membrane technologies provide a low-energy alternative to conventional filtration and chromatography methods, thereby diminishing the overall carbon footprint of the production process. The implementation of green chemistry principles and the design of bioprocesses that aim to reduce the waste generation and energy use are also vital for meeting the sustainability objectives.

1.6 Need to Shift to a Bio-Based Economy

The decline of fossil fuel resources is increasing the demand for biomass-based fuels and commodity chemicals. Therefore, new manufacturing methods that allow biomass to be converted into bulk and fine compounds in an environmentally responsible manner must be developed. The chemical industry is particularly affected by this paradigm shift because a variety of components are commonly created from materials with a petroleum base. In this case, organic solvents are great examples. The rise in demand is starting to affect the price of crude oil, which might have catastrophic consequences for world economies.

As our understanding of the many basic biological molecules grows, biotechnology advances. The petroleum-based economy is shifting gradually to the biofuels. It must improve the policies, financing, and legislation that nations are implementing. Biomanufacturing will then promote the engineering of living things to produce bioproducts. The bio factories will produce hydrogen, ethanol, butanol, bioenergy, and other biofuels in addition to raw materials for the building, automotive, and industrial sectors [34].

1.7 Biological Systems as a Biofactory

1.7.1 Bacterial Biofactory

A microbial cell factory, quick growth, and access to tools for gene and genome engineering, the well-established high cell density culture techniques, and an abundance of metabolic engineering systems are just a few advantages of E. coli, the most researched organism [35]. Its limited metabolic engineering systems are just one of its many drawbacks. Pseudomonas putida KT2440, a TOL plasmid-cured strain of Pseudomonas putida mt-2 is a frequently used strain. A novel bacteria called Pseudomonas putida is being assessed for use as an industrial host [36, 37]. Because it has specialized mechanisms that allow it to break down a wide range of dangerous substances in highly contaminated environments, it is very common [38]. The capacity of Pseudomonas species to create medium-chain-length polyhydroxyalkanoates makes them one of the most efficient biopolymer producers (PHAs) [39]. Numerous studies have been conducted on bacillus subtilis, an aerobic bacterium, because of its capacity to synthesize a variety of heterologous proteins. B. subtilis has demonstrated the productive expression of several enzymes, including lichenase, amylases, xylanases, and galactosidase. Through fermentation processes, bacillus subtilis can produce bacterial cellulases, proteases, and other enzymes [40].

1.7.2 Yeast Biofactory

Yeast has been used to produce wine, beer, and bread since the dawn of human civilization. It has, however, recently become one of the most well-known organisms that work as a sort of cell factory to produce various chemicals, medications, food ingredients, etc. [41]. Yeast cells are quite interesting since they are often utilized as model organisms to improve our understanding of human cells. Pichia pastoris, saccharomyces cerevisiae schizosaccharomyces, kluyveromyces lactis, and hansenula polymorpha are among the various yeast types employed in biomanufacturing [42]. Yeast is used to produce a wide range of goods, such as biofuels [43], and virus-like particles (VLPs), which are used to make vaccines [44], biopharmaceuticals, etc. The eukaryotic microbe yeast can produce post-translationally altered products, such as N-glycosylated molecules [45], which sets it apart from other eukaryotic organisms. In addition to their ability to be successfully grown at high concentrations, yeasts also provide scalable fermentation, rapid growth, a lower risk of contamination, easy genetic modification, and a more economical process.

1.7.3 Insect Cell Biofactory

In vitro insect cell culture has been extensively utilized since approximately 1950. Due to the ability to modify baculoviruses through biotechnology and use them as vectors, the infection of lepidopteran cell lines within a lytic system has facilitated the expression of heterologous proteins. The insect cell baculovirus expression vector system, or IC-BEVS, serves as a crucial facility to produce recombinant proteins and viral particles, which are essential for the development of valuable products. This underscores the importance of cell culture and gene transfer vectors [46, 47]. With superior glycosylation characteristics over other model systems, BEVS was created as a substitute for mammalian expression methods, and insect cells have produced a vast array of proteins [48]. During the initial phases of drug research, this is a common mode of expression. The yield would be lower than with a mammalian system due to the variable glycosylation pattern [49], even though desired commodities might be produced on a big scale using its vector technology.

1.7.4 Mammalian Cell Culture

Instead of using recombinant DNA (rDNA) in bacterial culture, certain biotechnology products, such viral vaccines, must be made using mammalian cells. The reason for this is because many complex proteins include glycan molecules through post-translational modifications. Biopharmaceuticals including enzymes and hormones, as well as immunobiological products like interleukins, lymphokines, and monoclonal antibodies, can be produced using rDNA technology in mammalian cell culture [50]. First-generation vaccines and replacement hormones were the first biopharmaceuticals to hit the market. Second-generation vaccines, recombinant proteins, and monoclonal antibodies came next. The COVID-19 pandemic has prompted major biotechnology and pharmaceutical companies to create a number of licensed or in-development COVID-19 vaccines or antiviral medications. Since cell culture is such an important part of drug development and manufacture, there is a greater need for cell culture products [51].

1.7.5 Biosensors

A biosensor is a measurement tool made up of an electrical system, transducer, base material, and bioreceptor [52]. To identify biological, organic, and inorganic chemical substances, it uses certain metabolic processes to generate electrical, thermal, or optical signals. The following are the many kinds of biosensors made from different organisms [53].

(i) Acetylcholinesterase Inhibition-Based Biosensors

Since the 1960s, organophosphorus pesticides (OPs) have been shown to be the most effective in maintaining agricultural productivity due to their high pest toxicity, ease of manufacture, and low production costs. Overuse of OP, however, could result in bioaccumulation in the environment, which would be a serious environmental issue. Furthermore, OPs phosphorylate acetylcholinesterase, irreversibly inhibiting it and potentially leading to neurological problems [54]. Researchers have developed a number of acetylcholinesterase inhibition-based biosensors to identify OP residue.

(ii) Microalgae Biosensors

Anthropogenic contamination is unavoidable when the industrial and agricultural sectors incorrectly discharge chemical waste into the soils, water, and air. A sustainable approach employing microalgae biosensors could be an advantageous option for the environment because of their availability, affordability, and disposability [55]. Additionally, a novel fluorometric biosensor chip based on the pseudokirchneriella subcapitata strain was created [56], that can rapidly identify a range of herbicides. Diuron, simetryn, simazine, and atrazine are the four herbicides that this biosensor chip is most sensitive to. Using a non-genetically modified strain of chlorella vulgaris, a bioluminescent microalgae biosensor was created [57], for the rapid detection of both light metals, like sodium, aluminum, and lithium, and heavy metals, like copper, lead, and cadmium.

(iii) Yeast-Based Biosensors

Indeed, a few cellular characteristics and molecular processes, such as numerous signalling pathways that are critical for identifying and reacting to environmental stimuli, are shared by yeast and mammalian cells. Interest in researching biosensing technologies has increased because of these advantages of yeast. For hormone detection, a fluorometric biosensor would be employed to accurately identify androgens, progestogens, and estrogens [58].

1.8 Progress in Biomanufacturing

It is believed that antibody-presenting viral nanoparticles (VNPs) hold great promise as a therapeutic and diagnostic tool. To exhibit nanobodies [59], two representative members of the genus Potyvirus—Tobacco etch virus and Zucchini yellow mosaic virus—can be used to produce genetically encoded viral nanoparticles that act as nanoscaffolds.

CdS quantum dots could be biomanufactured by employing directed evolution to develop a strain of stenotrophomonas maltophilia (SMCD1) that can make CdS nanocrystals extracellularly to aid in purification. Utilizing the biomanufacturing technique demonstrated here, the CdS semiconductor nanocrystals exhibit photoluminescent properties [60], and a size-dependent band gap. Although it will take advancements in our ability to predictably engineer plant biology, it is feasible to construct plants in space for the ideal biomanufacturing platform that can produce medications and biomaterials on demand. Small amounts of seeds can be kept viable at room temperature for many years, unlike microbes, which need to be preserved at below-freezing temperatures. Because they can repair their own carbon through photosynthesis mechanisms, plants just require CO_2 to grow [61]. Mannitol, a readily available component of seaweed and a promising feedstock for biomanufacturing, has a higher energy content than glucose. Mannitol can be converted by engineered microbes into several different bioproducts [62]. The ability of computers or machines under computer control to accomplish tasks that are comparable to those carried out by humans is known as artificial intelligence (AI). To attain the necessary titres, rates, and yield, a fully working AI would identify the best compounds to make, offer possible production routes, choose the ideal pathway configuration, and evaluate experimental data to correct the attempt. Machine learning in bioinformatics [63], refers to the use of machine learning methods in bioinformatics fields like as text mining, systems biology, microarrays, proteomics, evolution, and genomics. CRISPR/Cas has become a novel tool for metabolic pathway engineering in certain microorganisms [64], by altering the metabolic flux in the direction of the production of important biomolecules.

The exciting and novel field of biofabrication is being studied by tissue engineering and regenerative medicine. Biofabrication employs automated processes, such as additive manufacturing technology, to produce 3D biomaterial-based cell culture systems. Biofabrication is characterized by biological products, bio-inspired manufacturing processes, and cell-based building blocks. Because of this, most bio-products made by biofabrication are stem cell and biomaterial hybrids, including scaffolds, microcarriers, and microgels [65].

A branch of industrial biotechnology known as "biomanufacturing" is related to biological systems to generate high-value goods like biochemicals, biofuels and medicines. Improvements in technology and the fundamental understanding of biological mechanisms have driven important progress in this field. Key areas of development include single-use technologies, synthetic biology, the integration of automation with digital tools, and continuous biomanufacturing.

(i) Continuous Biomanufacturing

Traditional batch processing has transformed to continuous biomanufacturing. In continuous biomanufacturing, the inputs and outputs are in a constant flow as the production process remains uninterrupted. Enhanced productivity, consistent product quality, and reduced manufacturing times are merely a few advantages of this approach. The steady-state characteristics of continuous processes consent for the greater control over production conditions, which in turn increases lower costs. The production of biopharmaceuticals is an important application of continuous biomanufacturing. The reliable and highly effective production of therapeutic proteins have been enabled by continuous upstream processing methods, such as perfusion culture systems. To ensure an efficient production flow, downstream processes like filtration and continuous chromatography have also been advanced to complement continuous upstream systems. It presents the extensive benefits over traditional batch methods and has demonstrated the potentiality in the production of the biologics and monoclonal antibodies.

(ii) Integration of Digital Tools and Automation

The integration of digital tools and automation has pointedly improved the reliability and efficiency of biomanufacturing processes. Sophisticated control systems, data analytics, and sensors facilitate the real-time production monitoring and optimization. These technologies enable the precise control of input variables such as nutrient levels, temperature, and pH, ensuring optimal conditions for product synthesis and cell growth. Biomanufacturing is leveraging artificial intelligence (AI) and machine learning (ML) to envisage and improve the process performance. These tools can analyze the large datasets during the generation production time to identify trends and patterns that allow for proactive adjustments. AI-driven predictive maintenance decreases downtime and aids prevent equipment failures, further improving operational efficiency.

The perception of the "digital twin" is also being exploited in biomanufacturing. A digital twin, which is a virtual representation of a physical manufacturing system, is formed using advanced modeling techniques and real-time data. This digital model can be applied to test new perceptions, identify issues, and optimize and simulate production processes without disrupting ongoing operations. Digital twins hold the potential to improve scalability, industrial efficiency, and process development.

(iii) Sustainable Biomanufacturing

A substantial aspect of modern biomanufacturing is sustainability. The primary objectives are to improve the economic feasibility of biotechnological products and to diminish the environmental impact of production methods. Innovations in this area include waste reduction strategies, the use of renewable feedstocks, and energy-efficient production techniques. One approach to sustainable biomanufacturing includes waste and by-products as feedstocks for microbial fermentation. Substrates for microbial growth can comprise industrial byproducts, food waste, and agricultural residues, which helps to decrease the reliance on fossil fuels and substitute a circular economy. This method not only decreases the overall carbon footprint of biomanufacturing but also enhances the value to waste materials. Energy efficiency is another significant element of sustainable biomanufacturing. By advanced separation and purification methods, optimal process conditions and developing more efficient bioreactor designs, energy consumption can be significantly minimized. For instance, the membrane technologies improve the sustainability of biomanufacturing procedures by offering a low-energy substitute to chromatography techniques and traditional filtration.

1.9 Case Studies of Innovative Bioprocesses

Case studies focusing on advanced bioprocesses provide the remarkable understandings into the benefits and applications of industrial biotechnology. These instances demonstrate the impact of biotechnological improvements on industrial operations by showcasing successful applications across various fields.

(i) Insulin Production through Recombinant DNA Technology

The application of recombinant DNA technology for the production of human insulin stands out as one of the most important case studies. Before the initiation of biotechnology, the insulin was extricated from the pancreases of cows and pigs for diabetes treatment. In 1982, Genentech and Eli Lilly effectively generated the first recombinant human insulin by applying genetically modified E. coli bacteria, resulting in insulin that mirrors the production of the human pancreas. This breakthrough reduced the likelihood of allergic reactions and improved the availability of insulin, thereby altering diabetes treatment. The use of recombinant DNA technology not only improved the efficiency of insulin production but also enhanced its quality and safety. This case study represents how biotechnology can transform the pharmaceutical production and enhance the patient outcomes.

(ii) Bioethanol Production from Lignocellulosic Biomass

The production of bioethanol from lignocellulosic biomass, which assists as a sustainable substitute to fossil fuels, signifies an important case study. Traditional bioethanol production depends on the food crops such as sugarcane and corn, leading to concerns regarding food security and land use. Lignocellulosic biomass, agricultural waste, non-food plants, and sourced from wood offer a more sustainable feedstock for bioethanol production. Researchers have developed advanced bioprocessing methods to proficiently convert lignocellulosic biomass into fermentable sugars and subsequently into bioethanol. One of these methods includes the pre-treating the biomass to break down its complex structure, followed by the release of sugars through enzymatic hydrolysis. These sugars are then fermented into ethanol utilizing genetically yeast and modified bacteria. The successful commercialization of this process by companies such as DuPont and POET-DSM has presented the viability of producing bioethanol from lignocellulosic sources.

(iii) Production of Plant-Based Proteins

Microbial fermentation has been applied to generate the plant-derived proteins in reaction to the increasing demand for sustainable food options. Industrial biotechnology has been applied by companies such as Impossible Foods and Beyond Meat to develop meat substitutes that imitate the texture and taste of actual meat. Heme proteins generated through yeast fermentation are combined into plant-based components such as pea and soy protein to improve these products. Genetically modified yeast strains are used in the fermentation process to create heme, the chemical that gives meat its distinctive flavor and color. This invention has addressed ethical and environmental issues related to cattle rearing in addition to offering a sustainable substitute for animal flesh. The popularity of plant-based meat substitutes shows how biotechnology can revolutionize the food industry.

1.10 Overview of Biomaterials

The value and usefulness of metallic materials and their composites have been clear since the early 19th century. Significant progress has been made in the field of synthetic materials to understand how biomaterials interact with the human body and how to use them effectively [66, 67].

Since then, biomaterials—which are artificial—have been widely employed to replace or restore the many biological functions of human tissue. Because they constantly come into contact with bodily fluids, they aid in enhancing everyday human activities. The designed material should be examined for the same or distinct qualities required for its precise use through engineering design. When designing biomaterials, one crucial factor, that is, biocompatibility should be considered together with the material's chemical, physical, and mechanical properties, including whether it is bioactive, bioinert, or biodegradable [68].

In recent years, biotherapy employing these biomaterials has gained more traction in the prevention of several deadly illnesses, including cancer, heart infections, and AIDS. Combining basic science with practical applications, biotherapy has the potential to be a powerful treatment for fatal and incurable illnesses [69–71]. Biotherapy is mostly linked to the prevention of fatal illnesses using biotechnology or bio-based medications, including the identification of therapeutic targets through pathological analysis and the development of biotechnology related to immunotherapy, liver, etc. While immunotherapy is the use of vaccinations and antibodies to prevent disease, gene therapy is the intentional modification of gene expression in a specific tissue for the prevention of pathological diseases. The main conditions that can be treated with stem cell treatment are malignancies, hematological illnesses, cardiovascular disorders, etc. [72–75]. Furthermore, bone marrow transplantation is becoming a widely accessible stem-cell treatment. Tissue engineering is a rapidly expanding area of biomedical technology that makes it easier to regenerate and repair damaged tissues.

Biomaterials can be divided into two main classes based on where they come from: natural and synthetic (man-made). Natural biomaterials, such as gelatin, hyaluronic acid, heparin, and alginate, have been used for many years. Furthermore, because they are needed in big quantities, synthetic biodegradable polymers are currently being considered because of their wide-scale manufacture and simplicity of manipulation [76].

1.10.1 Biomaterials Classification

Categorization of biomaterials: Although many natural materials and their alloys are used in industry, only a small number of them demonstrate biocompatibility; as a result, they have outstanding bio-functionality and may be used as implantation materials in the future [77]. Table 1.1 explains some important traits and applications of different biomaterials.

1.10.2 Features of Biomaterials

The kind of medical application determines the requirements for biomaterial design and selection criteria. To have a strong use in the biomedical area for a longer period of time without immune rejection, the biomaterial needs to possess certain special qualities. Here are some descriptions of these traits [78, 79].

1. Exceptional biocompatibility
2. Adequate mechanical characteristics
3. Superior physical and chemical attributes
4. Sufficient wear resistance
5. Adequate rust resistance
6. Osseointegration (For bone implants)

Table 1.1 Important applications of biomaterials.

Sl. no.	Materials	Applications
1	Metals (such as stainless steel, Ag, Au, Ti and its alloy, etc.)	Weight-bearing implants include wires, joint replacements, screws, dental root implants, bone plates and pins, etc.
2	Ceramics, such as hydroxyapatite, zirconia, and alumina	Covering for dental and orthopedic implants, medical sensors, load-bearing implants, etc.
3	Polymers (such as polyester, silicon, and nylon)	Heart valves, blood vessels, artificial hearts, hip joints, contact lens sockets, etc.
4	Composites/Bio composites	Dental implants, bone cement, and joint replacements.

1.10.3 Applications of Biomaterials

Biomaterials are used in a wide range of industries, including pharmaceutical firms, food processing facilities, fashion design, and other home products. Biomaterials are widely used in the medical sciences for the creation of tissue scaffolds, implants, prostheses, and dental fixtures.

(i) Cardiovascular biomaterials

Certain heart conditions have a significant negative impact on people's quality of life and cannot be adequately treated with medication alone. As a result, the patient urgently needs supportive therapy that aids in improving their health. The usage of "biomaterials" is one such new treatment. These biomaterials can aid in the effective construction and implantation of vascular grafts and heart valves in cardiac diseases. Cardiovascular biomaterials (CB) are materials that are used as implants in conditions affecting the heart and that efficiently work with biological machinery. These days, there is a high need for cardiovascular biomaterials because of their success. Metals, polymers, and biological materials are the three groups into which these cardiovascular biomaterials can be divided. The type of impairment or injury determines the properties of the cardiovascular biomaterial utilized. For example, polymers have been the therapy of choice for cardiac damage; however, blood compatibility may provide issues. To solve this issue, certain novel technologies, such as surface changes, are now being investigated and used.

(ii) Blood vessel prostheses/vascular grafts

Blood vessel prostheses are the most widely used device for treating damaged or compromised blood vessels. Furthermore, vascular bypass, sometimes referred to as vascular graft technology, is a surgical technique that reopens blood channels to allow blood to freely flow from one location to another, reducing the effects of obstruction. It's a common procedure that involves avoiding the blocked blood channel or vessels to maintain normal blood flow between two healthy locations. The best material for this vascular bypass operation is either the patient's own vein (autograft) or a donor vein (allograft). In addition to them, polytetrafluoroethylene, or PTFE (teflon), and polyethylene terephthalate, or dacron, are also widely employed.

(iii) Heart valves

Nowadays, patients with valvular heart disease are treated by having an artificial heart valve implanted. This condition arises when the functioning of any one of the four heart valves is compromised. These prosthetic heart valves are divided into two categories based on how they work: biological and mechanical. PTFE, Dacron, and other synthetic materials or components of biological origin are used to make biological valves. Conversely, metals, polymers, and ceramics—such as silicone, titanium, stainless steel, and pyrolytic carbon—are used to make mechanical heart valves. Transcatheter aortic valve implantation has recently been accomplished using biological material (pig heart valve) and metals, ceramics, and polymers (titanium, stainless steel, and Dacron) [80].

(iv) Stents

The clogged blood channels supplying the heart with oxygenated blood are opened or bypassed by a stent. These stents, which can be either plastic or metallic, are placed into the blood vessel lumen. Stents come in various varieties, including urethral, coronary, prostatic, vascular, esophageal, and biliary stents, depending on the needs [81]. These stents can be divided into three groups based on their distinct physical and functional characteristics: drug-eluting stents (DES), bioabsorbable stents, and bare-metal stents (BMS).

(v) Artificial ligaments and tendons

The musculoskeletal system is supported and given stiffness by specific connective tissues, such as ligaments and tendons. Artificial tendon and ligament replacement is urgently needed when these tendons and ligaments are destroyed as a result of an accident or sports injury. However, it should be remembered throughout the implantation procedure that these synthetic tendons and ligaments need to share structural, functional, and biochemical traits with their natural counterparts. In order to withstand the body weight immediately following implantation, the biomaterial employed to create these artificial tendons and ligaments needs to possess sufficient mechanical strength [82].

(vi) Bone cement

A biomaterial called bone cement is utilized to bridge the space between the prosthetic and the bone. This bone cement is essentially made up of two parts: a liquid (MMA monomer) that serves as an inhibitor and a powder (pre-polymerized PMMA/PMMA copolymer beads) that functions as an initiator. The process of free radical polymerization is started when the initiator is added to the accelerator, changing the cement's viscosity and turning it into a hard substance [83]. The biomaterial utilized to fill in the gaps must mostly consist of bioresorbable material that promotes the growth of new bone in the injured location. CaP-based bioceramics are the most widely utilized biomaterial for bone regeneration because of their superior biocompatibility, osseointegration, and osteoconduction properties [84]. Hip implants are the most typical instance of CaP.

1.11 Manufacturing Process for Porous Implants

A popular fabrication approach for creating porous implants is the powder metallurgy method, which provides fine control over mechanical characteristics and porosity. Space-holder substances like ammonium bicarbonate or sodium chloride are integrated with metal particles like its alloys or titanium in this method. The combination experiences a sintering process, where high temperatures fuse the metal particles without melting them, after they have been crushed into the desired shape. The space-holder materials decompose during the sintering process, resulting in a porous structure in their place. This controlled porosity is vital for promoting osseointegration, as it allows for vascularization and bone ingrowth. Moreover, other methods that provide unique advantages regarding interconnectivity, customization, and pore size distribution, such as electrospinning, additive manufacturing and freeze casting are presently under investigation. Among these approaches, additive manufacturing is progressively favored due to its ability to create intricate geometries and patient-specific designs with controlled internal architectures, thereby improving the biological and mechanical performance of the implant.

1.11.1 Powder Metallurgy

A popular production method for generating porous implants is powder metallurgy, which provides the exact control over the material's microstructure and porosity. This procedure integrates metal powders, compacts them into the essential shape, and then sinters the compact at temperatures much below the underlying material's melting point. Particle bonding is controlled by the sintering process while maintaining the porosity structure, which is energetic for biomedical applications. Because it improves tissue integration, assists the bone growth, and increases the mechanical compatibility between the natural bone and implant, porosity in implants is vital. By adapting the powder properties, sintering parameters and compaction pressure, the pore interconnectivity and degree of porosity can be customized. Powder metallurgy regularly uses materials like its alloys and titanium because of its exceptional corrosion resistance, biocompatibility and mechanical strength. All things considered, powder metallurgy is an adaptable and economical technique for generating intricately shaped, porous implants that satisfy the functional needs of orthopedic and dental applications [85].

1.11.2 Additive Manufacturing

In the field of biomedical engineering, additive manufacturing (AM) has developed as a groundbreaking production technique, particularly for the development of porous implants. Unlike traditional subtractive manufacturing methods, additive manufacturing (AM) empowers the construction of highly tailored structures layer by layer from digital blueprints. This ability, which emulates the mechanical properties of natural bone, is particularly valuable for manufacturing implants with controlled porosity, an energetic factor for promoting osteointegration, enhancing nutrient flow, and dropping stress shielding. Various methods such as Selective Laser Melting (SLM), Fused Deposition Modeling (FDM), and Electron Beam Melting (EBM) are commonly applied to generate polymeric and metallic implants with changing pore shapes, sizes, and distributions. Due to their mechanical strength and biocompatibility, materials like cobalt-chromium alloys, biodegradable polymers and titanium alloys are often utilized. AM's design versatility allows for the making of implants featuring gradient porosity and interconnected pore networks, both of which are vital for long-term stability and vascularization. Despite challenges such as complying with regulatory standards, optimizing post-processing procedures, and ensuring consistent quality, additive manufacturing remains to boost improvements in implant design. Its capacity to generate functionally graded, the patient-specific porous implants signify an important advancement in the fields of personalized and regenerative medicine [86].

1.11.3 Electrospinning

For producing porous implants, electrospinning is a popular production method, especially in the fields of regenerative medicine and tissue engineering. By exposing a polymer solution or melt to a high-voltage electric field, fine, and continuous fibers are formed. These fibers are then assembled on a grounded surface to generate a nonwoven fibrous mat. The resultant structure offers a highly porous architecture with linked pores and a high surface area, closely resembling the extracellular matrix (ECM) of real tissues. Electrospun scaffolds are perfect for promoting cell adhesion, proliferation, and differentiation because of their properties. Implants that are both biocompatible and biodegradable can be made using a variety of natural and synthetic polymers, including collagen, gelatin, polycaprolactone (PCL), and polylactic acid (PLA). Furthermore, by modifying processing parameters such as voltage, solution concentration, flow rate, and collector type, the porosity and fiber diameter may be precisely regulated. Although changes like multi-layering or the addition of nanoparticles can improve their mechanical qualities for possible use in bone regeneration, electrospinning is especially useful for producing porous implants used in soft tissue applications, such as skin, nerve, and vascular grafts. cost-effectiveness, the capacity to create ECM-like structures that support tissue regeneration, and scaling up and attaining consistent thickness in larger constructs, despite certain limits [87].

1.12 Investment and Strategic Alliances to Boost Commercial Biomanufacturing

1.12.1 Partnerships for Product Development

The development and uptake of biomanufacturing techniques can be greatly accelerated by strategic alliances. Platform businesses like Amyris, Zymergen, and Ginkgo Bioworks present fresh chances for cross-industry application co-development. Significant scale and cost advantages for new development work are provided by collaborating with and engineering on platforms created by these kinds of businesses. Furthermore, industry experts can assist in guiding development towards the most crucial key performance indicators (KPIs) for product success for application-focused biomanufacturing startups founded on substantial experience in a specific technology area, such as Modern Meadow, Impossible Foods, and Bolt Threads.

(i) Cell development toolkits

Platform businesses make use of economies of scale inside a certain technology ecosystem that can support a wide range of applications. As a stand-in, the majority of computer software applications are created using a standard toolkit on a distinct platform, and the software is separated from the application. Similarly, platform firms are making the bioeconomy more accessible as basic biological unit activities become more standardized. For instance, Ginkgo Bioworks is creating a platform for cell programming to facilitate the engineering of biology. To facilitate the development of new products in close collaboration with product-oriented companies that lack in-house capabilities for large-scale biological engineering, their platform compiles an exhaustive list of the infrastructure, personnel, and tools required by businesses to design and develop microbes for new applications.

To reduce the barrier to creating new biomanufacturing apps, Ginkgo has launched Cell Development Kits (CDKs), which are the biological counterpart of software development kits used to create applications for iOS and Android. Pre-engineered cells are optimized for absorbing DNA libraries, instruments for creating and printing new DNA sets, specialized machinery for creating and cultivating the engineered organisms, and the automation, know-how, and infrastructure required to assess and validate bioprocess performance are all included in cell development kits. These platforms provide substantial cost savings for biomanufacturing when compared to the substantial time, money, and human commitment needed for new biomanufacturing companies to start producing material to evaluate novel applications. Technology pioneers find it particularly alluring to test and develop early theories without having to make significant financial investments. Larger businesses also used these kinds of technologies to investigate novel biomanufacturing approaches without having to worry about setting up labs and staff. CDKs are anticipated to shorten development durations from years to a few months in addition to saving money.

(ii) Sustainable product performance

Currently, the rate of application testing and product development required to bring a product to market does not keep up with the pace of upstream biomanufacturing advances, which refers to the biological manufacture or fermentation of a molecule. Although they are not always the most qualified to guide the subsequent procedures to purify, isolate, and manufacture a completed product from that molecule, synbiotechnology pioneers frequently contribute extensive technical experience to the manufacturing of a class of molecules. Technology innovators have a great chance to get the input they need on key upstream KPIs for successful deployment through strategic alliances with established product firms, while traditional manufacturers can quickly embrace a biomanufacturing approach. Genomatica and Lululemon announced their collaboration in 2020 to create a sustainable bio-nylon.

The $10 billion global nylon industry is based on the petrochemical derivative caprolactam [88]. Genomatica and Lululemon are collaborating to create caprolactam sustainably by fermenting plant sugars in a microbe. This presents a chance to get rid of the 60 million tons of nitrous oxide, a dangerous greenhouse gas that is normally produced by the production of petrochemicals. Genomatica has a great deal of experience developing biomaterials, and it is likely to hasten the use of sustainable biomaterials going forward while gaining from the product knowledge of seasoned producers like Lululemon. The production of bio-nylon uses a lot less energy and water than petrochemical alternatives, which gives it a competitive sustainability edge. It also dramatically lowers greenhouse gas emissions. The intrinsic sustainability of the bionylon production process turns into a "performance" indicator that has retail value for customers of Lululemon's premium goods even in the absence of improved material performance. Leveraging the sustainability advantage targeted at high-margin and luxury consumers may be a practical way to offset the upfront costs associated with the development and uptake of biomanufactured products.

(iii) Collaborations in manufacturing technologies

More companies are finding it economically feasible to use sustainable and cutting-edge materials as the cost of biomanufacturing applications keeps falling. Pharmaceuticals are often manufactured on a smaller scale (less than 1000-liter tanks), with greater manufacturing costs that are offset by the large profit margins. The production expenses of commodity chemicals, like bioethanol, are spread across larger batch sizes, allowing them to attain positive economics at large volumes (>200-kiloliter tanks). Until a market is sufficiently established to sustain scaled-up production, many potential biomanufacturing applications find it difficult to reconcile the high expense of producing at comparatively smaller levels. As the efficiency of these bio-transformations increases due to advancements in biological sciences, biomanufacturing costs are anticipated to continue declining. Partnerships with manufacturing technology partners can also result in significant synergies, even though they can also hasten the market acceptance of specific applications.

Partnerships that combine advances in synthetic biology with current manufacturing techniques, for example, are crucial to accelerating product development and testing required to commercialize these difficult applications, such as biomaterials. Modern Meadow is a synthetic biology startup platform that uses protein engineering and design to create sustainable performance materials through biofabrication. Today, Modern Meadow has concentrated its technological efforts on creating Bio-Alloy, a patented application platform that combines biopolymers and tailored proteins. In comparison to conventional leather, the Bio-Alloy technology offers several mechanical and thermal benefits while lowering greenhouse gas emissions by 60–85%, making it possible to make a strong entry into the materials market. To further speed up the implementation and uptake of the latest generation of performance biomaterials, Modern Meadow established a joint venture collaboration, BioFabbrica, with renowned Italian textile and materials supplier Limonta this year. BioFabbrica is prepared to provide sustainable biofabricated material solutions that satisfy the distinct performance and design requirements of brands by fusing Limonta's vast experience in state-of-the-art materials manufacturing techniques with Modern Meadow's patented Bio-Alloy Application Platform.

1.12.2 Expanding the Implementation of Novel Solutions

A large portion of the biomanufacturing capacity available today is focused on pharmaceuticals, which creates a difficult pricing structure for novel low-cost biomanufacturing applications. The infrastructure created for pharmaceutical applications is more advanced than downstream capabilities to chemically and physically separate targets for applications in alternative biomanufacturing domains. To guarantee equivalency and/or compatibility with the intended use, early prototyping is generally crucial in the commercialization of biomanufactured goods. If necessary, this would enable more upstream engineering cycles. For technology pioneers, the absence of this early prototyping turns into a significant hazard in bioengineering initiatives. For instance, gating to biomanufacturing applications is the availability of commercial demonstration scale for non-pharmaceutical uses. However, for early stage biomanufacturing goods, producing an initial prototype batch or maiden commercial production run presents a considerable logistical and financial hurdle. While historical leaders in fermentative manufacturing, such as DSM and Cargill, have achieved notable success in these kinds of applications, technology pioneers introducing novel manufacturing concepts to the market face a capital-intensive process in bearing the costs of development and manufacturing scale. Academic labs can now demonstrate small-scale processes, although their equipment and capabilities are frequently restricted. Large-scale solutions can also be provided by contract manufacturing companies, although working with these companies can be costly and necessitates pre-existing business need. The significance of having an in-house manufacturing footprint is also being diminished by advancements in the automation and sophistication of upstream process development technology (such as Sartorius' ambr250, Culture Biosciences, and Univercell), which allow for faster technology transfer across production.

(i) The biomanufacturing co-operative

Pre-competitive bioprocess demonstration facilities that are built with the flexibility of applications now possible are necessary, as evidenced by the dispersed status of pilot and prototyping capacities for biomanufacturing applications. Technology pioneers may be able to speed up application testing and prototyping through public-private initiatives like "biomanufacturing cooperatives," in which businesses jointly fund and co-design, hence raising the success rate of biomanufacturing applications overall. Applications in biomanufacturing have many upstream equipment requirements, which might facilitate market segment and biosecurity application variety. To cover the required range of applications and overcome a big obstacle to biomanufacturing prototyping, downstream capabilities are far more varied and demand careful design and substantial expenditure. The features of such a model are examined.

(ii) Co-operative design needs

Today, the majority of biomanufacturing prospects come from growing microorganisms in a stirred tank to carry out a biotransformation on inexpensive feedstock. Microbial fermentation is now the first step in the production of proteins for meatless burgers, compounds like caprolactam for bio-nylon, and the plasmid DNA starting material for COVID-19 vaccines.

Tank size, particular process control requirements, and regulatory compliance (such as oxygen feeds, solvent rating, and good manufacturing practice compliance) can vary depending on the application; nonetheless, the main capital components and capabilities are comparable. Although the biomanufacturing ecosystem shares the engineering biology toolbox, each product application has different processing requirements in order to meet the critical performance indicators for product success. As biological engineering capabilities mature, the pipeline of upstream bioprocess development to biologically create desired items is growing and speeding up. The downstream unit procedures necessary to separate the product and get it ready for product application cannot be generally described in the same way. A wide range of chemical, physical, and thermal unit activities are required to extract and process target products from biological systems for several uses outside of the biological component of biomanufacturing [89]. To guarantee minimal acceptable performance against fundamental product KPIs and prevent product integration issues following significant time and financial commitment, downstream development must be started as early as feasible in the biomanufacturing development cycle. The capacity to evaluate the newly obtained raw input in the product context—through nutritional research of novel ingredients, stress testing of biomaterials, and sensory testing of flavor and fragrances—is essential for the successful integration of biomanufacturing applications. Only once, all upstream and downstream unit procedures have been designed to purify and isolate the finished product are these application testing techniques feasible.

A lot of startups squander time and money building up a specialized manufacturing scale before confirming the targeted application's financial feasibility. To boost the rate of commercial biomanufacturing achievements, scaling partnerships present a chance to broaden the biomanufacturing ecosystem and combine complementary knowledge and technology. Collaborative initiatives, would pool the resources and knowledge required to support the deployment of biomanufacturing products. A significant obstacle to tech pioneers' commercialization of novel biomanufacturing applications will be removed with investment in the development of state-of-the-art, collaborative spaces and manufacturing resources, which will also hasten bioeconomic growth.

1.13 Challenges and Limitations in Bioprocessing and Biomanufacturing

To fully realize the potential of industrial biotechnology, several obstacles and constraints still need to be overcome, even considering the many developments in bioprocessing and biomanufacturing. These difficulties can be roughly divided into four categories: environmental, regulatory, economic, and technical.

(i) Challenges in Process Integration and Automation

There are advantages and disadvantages to incorporating new technologies like machine learning (ML) and artificial intelligence (AI) into bioprocessing and biomanufacturing processes. Although these technologies can improve predictive maintenance and process optimization, their deployment necessitates a large investment and level of knowledge. Extensive data gathering, model training, and validation are all necessary to ensure that AI and ML models are accurate, dependable, and applicable to actual bioprocesses. System integration and interoperability issues are also brought about by the automation of bioprocessing and biomanufacturing. Complex software and hardware solutions are needed to guarantee that various production system components, including bioreactors, sensors, and control systems, operate in unison. Furthermore, it is essential to keep automated systems flexible and adaptive in order to support various bioprocesses and production scales.

(ii) Environmental Challenges

Industrial biotechnology presents environmental challenges even as it provides more sustainable alternatives to conventional chemical processes. To reduce the impact on the environment, biowaste disposal, including fermentation wastes and discarded microbial cultures, must be controlled. High concentrations of organic matter and nutrients found in biowaste have the potential to pollute and eutrophicate water basins if improperly handled. Another important issue is feedstock sustainability. The sourcing and supply chain of biomass must be controlled to prevent adverse environmental effects, even though using renewable biomass as fuel is more sustainable than using fossil-based resources. For instance, if biomass feedstocks are not managed sustainably, their large-scale cultivation may result in deforestation, biodiversity loss, and changes in land use.

(iii) Economic Challenges

There are important financial barriers due to the high costs related to the raw materials, process development and bioreactor equipment. Bioreactors and other biomanufacturing apparatus often require the extensive initial investments. Moreover, the overall economics of bioprocessing can be profoundly influenced by the costs of raw materials such as growth media and feedstocks. Considerable expenses are also associated to optimization and process development, specifically in the creation of cell lines and microbial strains. The iterative nature of strain generation, which includes multiple rounds of genetic testing and modifications, further increases the financial resources and time required. Furthermore, the regulatory demands for biopharmaceuticals and other biotechnological products require the rigorous testing and validation to confirm the safety and effectiveness, leading to additional costs.

(iv) Technical Challenges

Enhancing the microbial strains and cell lines implies a significant technological challenge in bioprocessing. The optimization of metabolic pathways and comprehensive genetic engineering are crucial to attain higher efficiency, yet these systems can be intricate and time-consuming. Additionally, maintaining the steadiness of genetically modified strains in industrial environments is both challenging and critical. Strain instability can lead to productivity losses and variations in product quality. Another key technical challenge is the scalability of bioprocesses. While laboratory-scale processes can be precisely controlled and optimized, scaling them up to industrial levels often explores the variability and inefficiencies. At larger scales, the issues such as oxygen transfer, mixing, and heat removal become more noticeable, necessitating the advanced bioreactor designs and control systems.

1.14 Conclusion

Industrial biotechnology has been changed bioprocessing and biomanufacturing, leading to more active and sustainable production techniques. This study indicates advancements, key applications, and future prospects in the field, showcasing biotechnology's widespread impact across various industries. The historic development of industrial biotechnology reveals the evolution from traditional fermentation systems to advanced biomanufacturing approaches. The development of microbial strains has been pointedly improved through the integration of synthetic biology, genetic engineering, and genome editing technologies such as CRISPR-Cas9. This progress has empowered the efficient and precise production of bio-inspired materials. Innovations in bioprocessing, including new fermentation methods, novel bioreactor designs, and process analytical technologies (PAT) have enhanced the efficiency of biotechnological production. Continuous biomanufacturing and single-use technologies have made biomanufacturing more effective and accessible, while also improving flexibility, lowering contamination risks, and reducing costs. Industrial biotechnology is used in various sectors, including pharmaceuticals, food and beverage, biofuels, agriculture, and environmental management. Bioprocessing has facilitated the creation of sustainable biofuels, environmentally friendly bioplastics, life-saving biopharmaceuticals, addressing urgent global challenges such as healthcare, energy sustainability, and plastic pollution. Notable instances that demonstrate the practical and transformative potential of biotechnological innovations include the bioethanol from lignocellulosic biomass, production of insulin, and bioplastics derived from microbial fermentation. Despite these developments, numerous challenges and limitations remain. Technical hurdles, such as the improvement of microbial strains and the expansion of bioprocesses, necessitate ongoing research and development.

The sustainable bioprocessing and circular economy will continue to be significant areas of concentration, propelling initiatives to reduce their negative effects on the environment and increase resource efficiency. The sustainability of biotechnological production will be improved by the creation of green chemistry concepts, biorefinery platforms, and renewable feedstocks. New markets and prospects for industrial biotechnology will be created by emerging applications in specialty chemicals, sophisticated materials and food technology. The advancement of industrial biotechnology will require interdisciplinary and collaborative approaches. Innovative bioprocess development and commercialization will be facilitated by collaborations among academic institutions, industry, and regulatory agencies. The next generation of biotechnologists will be trained through interdisciplinary research and education programs that promote creativity and teamwork. In conclusion, by offering effective and sustainable manufacturing methods, industrial biotechnology has the potential to completely transform a number of industries. Bioprocessing and biomanufacturing have the potential to significantly improve healthcare, energy, food, and environmental management by tackling present issues and utilizing new trends. Industrial biotechnology's ongoing progress will be essential to tackling global issues and advancing sustainable development, which will lead to a more prosperous and sustainable future.

It has been noted in recent years that these biodegradable polymers have been widely used in biotherapy because of their biocompatibility and biodegradability. However, the higher standard for these biomaterials has been established following the development of recently developing fields like biotechnology and medical technology. Perfect biodegradable polymers with special properties are quite valuable. Synthetic biodegradable polymers have been discovered to have lower immunogenicity and to be highly amenable to chemical alteration when compared to natural biodegradable polymers. As a result, they may present new opportunities in the future.

In summary, the development of biomanufacturing has been a protracted and intricate process, with numerous significant discoveries and breakthroughs for the creation of goods in the biotechnology, pharmaceutical, food processing, and industrial areas, as well as new biomanufacturing applications, are constantly being explored. Many organisms have the potential to be biofactories, whether they be whole organisms, their cells, or extracts of bacteria, yeast, algae, plants, animals, and insects. The possibilities for biomanufacturing are almost endless with further study and advancement. Numerous sectors could undergo a transformation because of biomanufacturing. Biomanufacturing has made it possible to generate more economical, sustainable, and efficient goods that could benefit both the human health and environment. Biomanufacturing has the potentiality to play a bigger role in our economy and daily lives with extra study and development.

1.15 Future Prospects in Biomanufacturing

As a result of advancement in technological advancements, scientific research, and an increasing demand for sustainable solutions, industrial biotechnology is anticipated to experience considerable growth and change in the coming years. Various innovative concepts are persuading the areas of biomanufacturing and bioprocessing, offering potential enhancements in scalability, sustainability, and efficiency.

(i) Synthetic Biology and Genome Engineering

One of the most important areas for the future of industrial biotechnology is synthetic biology. This discipline combines engineering principles with biological concepts to generate and develop innovative biological tools, components, and systems. Recent advancements in synthetic biology have empowered the production of tailored microbial strains and cell lines with optimized metabolic pathways for the production of various products, including biochemicals, biofuels, pharmaceuticals, and food ingredients. The field of genetic engineering has been reformed by CRISPR-Cas9 and other genome-editing technologies, which facilitate precise modifications to cellular and microbial genomes. These methods improve the productivity and efficiency of bioprocesses by optimizing metabolic pathways and eliminating undesirable byproducts.

(ii) Incorporation of Artificial Intelligence and Machine Learning

The bioprocessing and biomanufacturing sectors are on the border of an important transformation because of the integration of artificial intelligence (AI) and machine learning (ML). The vast amounts of data created during production can be analyzed by AI and ML algorithms to identify trends, improve workflows, and envisage outcomes. By facilitating control of bioprocesses and real-time monitoring, these systems improve the productivity, lessen variability, and augment product quality. Moreover, AI-driven predictive maintenance can anticipate the equipment failures and schedule repairs proactively, minimizing downtime and ensuring uninterrupted production. Furthermore, AI-enabled process optimization can reduce the resource and energy consumption, thereby enlightening the sustainability of bioprocessing. It is projected that the application of AI and ML in industrial biotechnology will improve and exert a more important impact as these technologies change.

(iii) Industry 4.0 Technology Adoption

Bioprocessing and biomanufacturing are developing owing to the influence of Industry 4.0. Key components of Industry 4.0 being combined into biotechnological production include automation, improved data analytics, and the Internet of Things (IoT). Real-time information regarding process conditions can be attained from IoT-enabled equipment and sensors, facilitating precise control and optimization. Digital twins, which are virtual representations of actual production systems, are applied to improve bioprocesses. These digital models can assess various scenarios, identify potential issues, and refine process design without disrupting real operations. With the adoption of Industry 4.0 technologies, biomanufacturing is projected to become increasingly efficient, flexible, and scalable, thereby improving its ability to reply to changing production necessities and market demands.

(iv) Bioprocessing Sustainability and the Circular Economy

An important concern for the future of industrial biotechnology is sustainability. Efforts are currently being made to develop environmentally friendly and efficient bioprocesses. This includes the generation of biochemicals, bioplastics and biofuels from renewable feedstocks, such as agricultural byproducts and waste materials. Moreover, the application of green chemistry is a growing trend, which aims to reduce the use of harmful substances and decrease waste production. Bioprocessing is embracing the perception of a circular economy, which promotes the recycling and repurposing of waste resources within production processes. One efficient method to diminish waste and confirm a sustainable supply of raw materials is to apply the waste biomass as a feedstock for microbial fermentation.

(v) Teamwork and Multidisciplinary Methods

Interdisciplinary and collaborative methods that integrate knowledge from various fields, including chemistry, biology, data science, and engineering, will configure the future of industrial biotechnology. The development of new technologies, the progress of research, the safe and effective application of bioprocesses depend on the alliance among regulatory bodies, academia, and industry. Public-private partnerships can accelerate the development and commercialization of biotechnological novelties by enabling the sharing of resources, infrastructure, and expertise. Preparing the next generation of biotechnologists and nurturing a culture of innovation also deliberately relies on educational initiatives and interdisciplinary research.

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