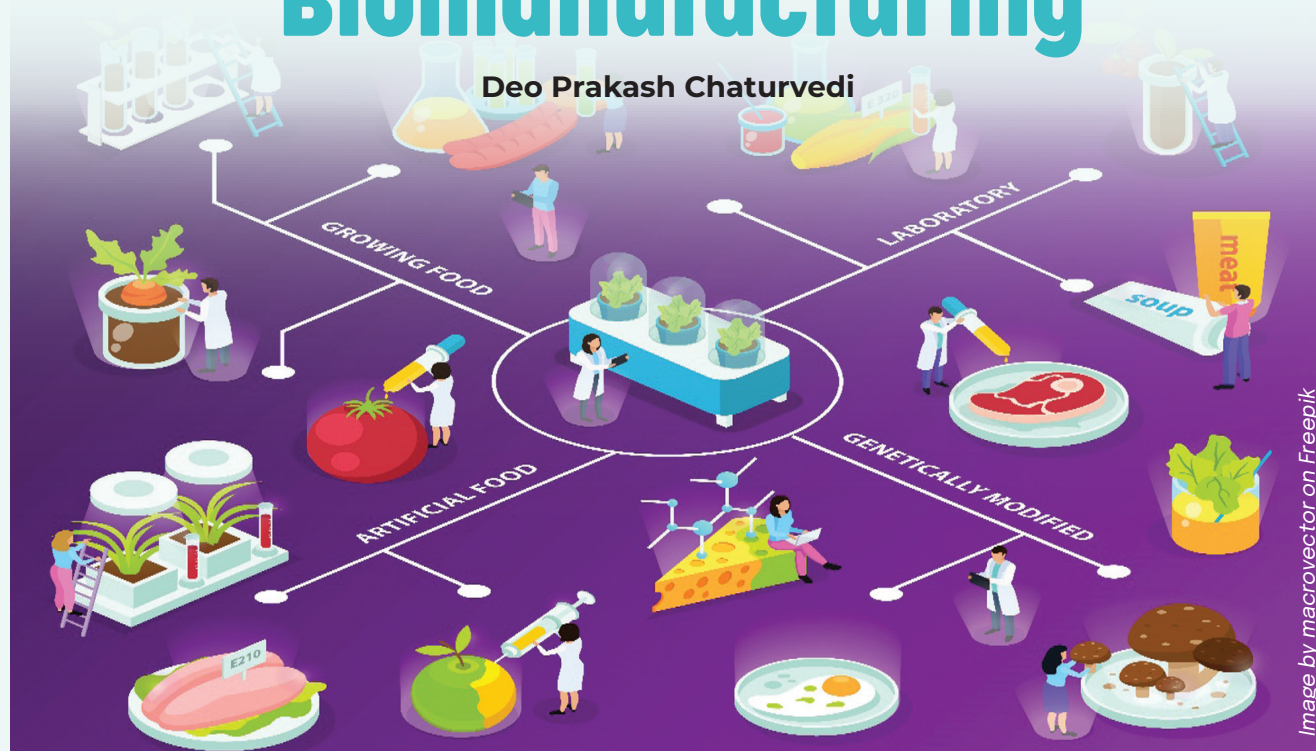


Revolutionising Industries

The Power and Potential of Biomanufacturing



INDIA'S bioeconomy is rapidly expanding and is projected to achieve a \$150 billion valuation by 2025, up from its \$80 billion value in 2021-22. The Indian government is actively fostering the growth of the bioeconomy and has made part of its National Biotechnology Development Strategy 2021-25. This thriving bioeconomy encompasses diverse fields such as agriculture, pharmaceuticals, food and beverages, chemicals, and energy. India's strengths in these sectors, along with its abundant skilled scientists and engineers and conducive innovation environment, provide a solid foundation for the bioeconomy's development. The COVID-19 pandemic has accelerated this growth by propelling India to the forefront of vaccine and biopharmaceutical production.

At the heart of propelling the bioeconomy forward lies the pivotal concept of biomanufacturing — harnessing the power of biological systems to craft products for the market. Biomanufacturing in India will not only slash the dependence on imported bio-based commodities, but it is also expected to act as a dynamic engine for job creation, economic revitalisation, environmental preservation, and innovation to address pressing global challenges like climate change and food security. A recent noteworthy development in this arena is the resounding emphasis placed by the Department of

Biotechnology (DBT), Government of India, on elevating the nation to a prominent hub of biomanufacturing excellence.



Dr Jitendra Singh inaugurated a discussion meeting to foster the Biomanufacturing Initiative of the Department of Biotechnology (DBT) in New Delhi in July 2023

Historical Development and Milestones

Biomanufacturing has ancient roots, dating back thousands of years when humans began to use fermentation processes to produce food and beverages. The earliest forms of

	Pre-modern BM	BM 1.0	BM 2.0	BM 3.0	BM 4.0
Products	Fermented products	Primary metabolites	Second metabolites	Proteins Enzymes	Renewable energy, New food, Better life
Methods	Mixed cultures + solid state ferment.	Mono-culture + anaerobic liquid ferment.	Mono-culture + aerobic liquid ferment.	rDNA tech + cell cultures	IPS + ME&SB + PE + ivSB
Key persons & time	 Louis Pasteur 1860s	 Chaim Weizmann 1910s	 Alexander Fleming 1940s	 Paul Berg 1980s	

Different phases of Biomanufacturing and important discoverer of each phase
Source: adapted from Zhang et al., 2017

biomanufacturing involved the fermentation of grains in producing beer and the fermentation of milk to yoghurt and cheese. Louis Pasteur pioneered fermentation technology and was a notable personality of this period. Based on the development of new technologies, the evolution of biomanufacturing can be categorised as follows:

- In Biomanufacturing 1.0, the focus lies on the production of primary metabolites through mono-culture fermentation. This approach, pioneered by Chaim Weizmann during World War I, utilises single strains of microorganisms to produce essential compounds like butanol, acetone, ethanol, citric acid, etc. These primary metabolites serve as building blocks for various industrial processes and are crucial for biofuel production, pharmaceuticals, and food additives.
- Biomanufacturing 2.0 takes the next step by concentrating on producing secondary metabolites. This involves using microorganisms to synthesise valuable compounds like penicillin and streptomycin. The process typically employs aerobic submerged liquid fermentation, providing optimal conditions for the growth and productivity of the microbes. Sir Alexander Flemings serendipitous discovery of penicillin in 1928 is considered the biggest breakthrough of this period.
- Biomanufacturing 3.0 introduces the production of large-size biomolecules, such as proteins and enzymes, by using recombinant DNA technology and advanced cell culture techniques. This paradigm shift allows for the production of complex biologics like erythropoietin, insulin, growth hormone, amylase, and DNA polymerase.

Significance and Objectives

Biomanufacturing stands out in several ways:

- **Sustainable Production:** biomanufacturing relies on renewable resources, reducing reliance on finite raw materials and fossil fuels. This supports sustainability and circular economy principles by minimising environmental impact.
- **High Specificity and Purity:** living organisms can produce intricate molecules with precision and purity, particularly beneficial in creating pharmaceuticals and bioactive compounds.
- **Cost-Effectiveness:** optimised biomanufacturing processes become cost-effective, especially for large-scale production of high-value goods.
- **Versatility:** biomanufacturing is adaptable, enabling the creation of diverse products like enzymes, biofuels, bio-based materials, cultured meat, etc.
- **Reduced Carbon Footprint:** bio-based products from biomanufacturing tend to have a smaller carbon footprint than their petrochemical counterparts, aiding in mitigating climate change.

These biomolecules find applications in medicine, biotechnology, and various industrial processes. The discovery of Restriction endonucleases by Werner Arber, Daniel Nathans, and Hamilton O Smith and, later on, Paul Berg's discovery of recombinant DNA technology in the 1970s are the most important drivers of this period.

- Biomanufacturing 4.0 embraces cutting-edge technologies to pioneer new product categories and improve existing ones. One revolutionary aspect is regenerative medicine, where human tissues and cells are engineered using stem cells and tissue engineering. This groundbreaking field offers unprecedented potential for organ transplantation, tissue repair, and personalised medical treatments.

Principles of Biomanufacturing

Biomanufacturing's success hinges on selecting suitable host organisms and microorganisms that act as production centres. These living systems are genetically modified to perform specific tasks, with the choice of host depending on the desired product. Like *Escherichia coli*, bacteria are favoured for their rapid growth and genetic manipulability, making them apt for producing small molecules and therapeutic proteins. Yeasts, notably *Saccharomyces cerevisiae*, also serve as hosts, producing proteins with modifications similar to higher organisms. Fungi like *Aspergillus* and *Penicillium* excel in generating enzymes, antibiotics, and complex molecules. Because of their intricate post-translational modifications, mammalian cells are vital for biopharmaceutical production.

Genetic engineering and synthetic biology are other important aspects of biomanufacturing. Genetic engineering provides a mechanism for altering an organism's traits by manipulating its genetic material. On the other hand, synthetic biology takes genetic engineering further, designing new biological components, systems, and functions. It uses standardised genetic parts to create intricate circuits and pathways, forming the basis for biomanufacturing.

Other indispensable aspects of biomanufacturing are employing quality control through stringent regulations, following safety protocols, and maintaining the efficacy of biomanufactured products. Regulatory bodies, like the FDA from the USA and CDSCO from India, supervise biopharmaceutical processes for adherence to Good Manufacturing Practices (GMPs).

Biomanufacturing in Pharmaceuticals

Biopharmaceuticals, a category of medicinal drugs sourced from living organisms, involve intricate molecules such as proteins and nucleic acids. These differ from the conventionally synthesised chemical molecules. The development of biopharmaceuticals initiates with identifying the disease-contributing biomolecules as potential therapeutic targets. Once identified, the relevant genes are cloned and inserted into host organisms, like bacteria or mammalian cells, to produce the desired therapeutic biomolecules.

Monoclonal antibodies (mAbs), designed to target specific cell or pathogen surface antigens, are produced using genetically engineered mammalian and other higher organism

cells capable of the necessary post-translational modifications. After purification, these proteins are formulated into injectable solutions for therapeutic applications. Effective against cancer, autoimmune disorders, and infections, mAbs offer high specificity and minimal side effects.

Biomanufacturing is pivotal in large-scale vaccine production to combat infectious diseases. Unlike traditional methods using weakened pathogens, biotechnology enables novel vaccines like recombinant subunit and mRNA vaccines. Recombinant subunit vaccines involve expressing pathogenic proteins in a host organism so that, after purification, they can be used as vaccine antigens. mRNA vaccines, revolutionary in approach, use synthetic RNA to prompt cellular production of viral antigens, activating the immune system without live viruses.

Therapeutic proteins, including cytokines, growth factors, hormones, and enzymes, are also produced using biomanufacturing. They treat diverse medical conditions, such as hormonal imbalances and genetic disorders, delivering targeted and effective treatments.

Advancing gene and cell therapies, reliant on biomanufacturing, hold promise for genetic disorders and specific cancers. Gene therapies deliver functional genes to correct mutations or provide therapeutic effects using viral vectors. Cell therapies modify patients' cells, like T cells or stem cells, enhancing their therapeutic capabilities before reintroduction. These therapies offer personalised and potentially curative treatments for previously untreatable conditions.

Biomanufacturing in Food and Beverages

In the food industry, the significant impact of biomanufacturing is evident through the advancement of alternative protein sources. As the demand for protein-rich foods rises and conventional livestock farming grapples with environmental and ethical concerns, biomanufacturing offers a feasible and eco-friendly substitute. Plant-based proteins, achieved via fermenting plant-derived materials, have gained traction as a sustainable alternative to conventional meat. Variants like soy, pea, and mycoprotein from fungi are processed into meat-like products, offering a sustainable choice with lower environmental impact, reduced greenhouse gas emissions, and decreased land and water usage. Another pivotal advancement is cultivated meat by growing animal cells in a controlled biomanufacturing setting, sidestepping the need for conventional animal farming. This approach can potentially deliver ethical and environmentally conscious meat sources while ensuring food security for an expanding global population.

Fermentation, an age-old biomanufacturing technique, has enjoyed extensive application in the food and beverage industry for centuries. This process involves the controlled microbial conversion of organic compounds, like sugars, into desired products. Fermented foods and beverages provide health benefits, enhanced nutritional content, and distinctive flavours and textures. Iconic examples include yoghurt, cheese, sauerkraut, pickles, beer, wine, sake, etc.

Major Initiatives to promote Biomanufacturing in India

1. **Make in India Campaign:** launched by the Indian government, this initiative aims to promote manufacturing across various sectors, including biotechnology. It focuses on attracting domestic and foreign investment to boost production and job creation.
2. **Biotechnology Parks and Clusters:** the government has established biotechnology parks and clusters in states like Karnataka, Telangana, Uttar Pradesh, etc. These parks provide infrastructure and facilities to support biomanufacturing companies, research institutions, and startups.
3. **Biotechnology Industry Research Assistance Council (BIRAC):** this is a Public Sector Unit (PSU) of the Department of Biotechnology; it supports research, innovation, and entrepreneurship in the biotechnology sector. It provides funding, mentorship, and resources to startups and companies involved in biomanufacturing.
4. **National Biotechnology Development Strategy 2021-25:** DBT launched a strategy to strengthen the biotechnology sector, promoting research and development, human resource development, infrastructure development, and regulatory reforms. The department has also set a target of achieving a \$150 bioeconomy by 2025.
5. **Skill Development Initiatives:** to address the shortage of skilled professionals in the biomanufacturing sector, the department of Biotechnology and other government agencies have initiated skill development programmes and training centres to train qualified workers.
6. **International Collaborations:** India has been collaborating with international organisations and countries to promote knowledge exchange, technology transfer, and investment in the biomanufacturing sector. DBT recently signed Implementation Agreement with the National Science Foundation, USA, in this connection.
7. **Startup Support:** various government-backed schemes and programmes support biotech startups, including funding, mentorship, and incubation facilities. The Atal Innovation Mission is an example of such an initiative.

Moreover, biomanufacturing enables the production of bioactive compounds with potential health advantages. For instance, certain microorganism-derived enzymes can enhance the texture and shelf life of processed foods. Antioxidants, abundant in fruits, vegetables, and select microorganisms, are crucial in counteracting harmful free radicals in the body, contributing to overall well-being. These bioactive compounds can be integrated into functional foods and beverages by harnessing biomanufacturing techniques, elevating their nutritional worth and health-enhancing properties.

Bioenergy and Sustainable Fuels

Bioenergy, harnessed from biological sources, presents an environment-friendly and renewable alternative to conventional fossil fuels. Central to this transition toward sustainability and low-carbon energy is the vital role played by biomanufacturing in the production of biofuels and sustainable fuels.

Biofuels, derived from organic materials like plant biomass, agricultural remnants, and waste, transform biomanufacturing processes into viable fuel options that can replace conventional fossil fuels such as gasoline, diesel, and aviation fuel. There are two primary categories of biofuels:

- **Bioethanol:** is an alcohol-based fuel originating from the fermentation of sugars extracted from crops

like sugarcane, corn, and wheat. Biomanufacturing techniques, encompassing fermentation and distillation, convert these sugars into ethanol. This bioethanol is frequently used as a blending element in gasoline, effectively reducing greenhouse gas emissions and fostering a more sustainable transportation sector.

- **Biodiesel:** produced from vegetable oils, animal fats, or recycled cooking oils, is another renewable fuel. Through processes like transesterification, biomanufacturing chemically transforms these oils and fats into biodiesel. As a cleaner and more ecologically sound alternative, biodiesel can directly replace conventional diesel, benefiting diesel-powered vehicles and machinery.

Beyond biofuels, biomanufacturing contributes to the production of biogas and biohydrogen, gaseous biofuels derived from organic matter through anaerobic fermentation. Biogas, primarily composed of methane and carbon dioxide, arises from organic waste materials such as food waste, agricultural remnants, and sewage sludge. Biomanufacturing enables microorganisms to break down organic matter by facilitating anaerobic digestion, releasing methane-rich biogas. Meanwhile, biohydrogen is generated through dark fermentation, where specific microorganisms ferment organic materials without light, yielding hydrogen gas as a clean and sustainable energy carrier. Upon combustion, biohydrogen

solely produces water as a byproduct. Both biogas and biohydrogen possess versatile applications, including electricity generation, heat production, and substitution for fossil fuels in diverse industrial processes.

Bio manufacturing in environmental protection

Biomanufacturing has significantly advanced biodegradable materials as eco-friendly alternatives to traditional plastics and other materials. These materials, derived from renewable sources, can naturally decompose, reducing the burden of solid waste like plastic and promoting a circular economy.

An important achievement within this field is bioplastics production through biomanufacturing. Bioplastics, sourced from starch, cellulose, or Polylactic Acid (PLA), find applications in various sectors. Starch-based bioplastics, made from plant starches like corn, are transformed through biomanufacturing into biodegradable plastics used in single-use items and food packaging. Cellulose-based bioplastics, obtained from plant fibres, are used in biodegradable films and coatings for packaging and biomedical purposes. PLA, derived from cornstarch, is processed using biomanufacturing to create environment friendly alternatives for items like food containers and 3D printing filaments.

Biodegradable medical devices are another outcome of biomanufacturing. These devices fulfil their functions within the body and degrade over time, eliminating the need for additional removal surgeries. Examples include biodegradable sutures, tissue scaffolds, and drug delivery systems.

Biomanufacturing also plays a pivotal role in environmental remediation through bioremediation strategies. Microbial bioremediation involves using bacteria, fungi, and microorganisms to convert pollutants into less harmful forms. Biomanufacturing enhances their effectiveness by enabling large-scale production. This approach helps remediate pollutants like petroleum hydrocarbons, heavy metals, pesticides, and solvents.

Biomanufacturing addresses plastic waste by engineering microorganisms and enzymes that break down plastic polymers. These plastic-degrading enzymes, produced through biomanufacturing by certain bacteria, aim to facilitate plastic waste degradation and improve recycling.

Furthermore, biomanufacturing is instrumental in creating biosensors, which use biological components to detect specific environmental substances. Biosensors are crucial in identifying pollutants like heavy metals and pesticides in air, water, and soil. They offer advantages such as sensitivity, quick response, and the detection of multiple pollutants. Bioluminescent biosensors, using bioluminescent bacteria, emit light in the presence of target substances, simplifying contamination assessment. eDNA monitoring utilises genetic material from the environment for biodiversity assessment.

Bio manufacturing in Agriculture and Crop Improvement

By leveraging biotechnology and biomanufacturing techniques, scientists have innovatively enhanced crop yield,

bolstered resistance against pests and diseases, and advanced eco-friendly farming practices.

Genetically Modified Organisms (GMOs) exemplify biomanufacturing's impact on agriculture. GMOs are organisms with ingeniously altered genetic material that introduce targeted traits. In agriculture, GMOs have versatile applications, particularly in improving crop attributes:

- **Pest Resistance:** GMO crops produce insecticidal proteins, acting as natural pest deterrents, reducing reliance on chemical pesticides. Genes from *Bacillus thuringiensis* (*Bt*) have been integrated into crops like corn and cotton, protecting against specific insect pests.
- **Herbicide Tolerance:** GMO crops tolerate specific herbicides, aiding weed management without harming crops.
- **Disease Resistance:** GMO crops express genes for resistance against plant diseases, enhancing crop resilience and minimising yield losses.

Plant tissue culture and cloning are biomanufacturing techniques transforming agriculture. Plant tissue culture grows plant cells, tissues, or organs in controlled environments, generating identical plantlets from small tissue segments. This is vital for propagating scarce varieties and producing disease-free planting materials. Cloning creates genetically identical offspring, swiftly yielding plants with desirable traits like high yield or disease resistance.

RNA interference (RNAi) technology is another biomanufacturing innovation. It silences specific genes through small RNA molecules, benefiting crop improvement and pest control. RNAi enhances crop resistance by introducing RNA molecules that target essential genes in pests, curbing their viability and survival.

Challenges

In biomanufacturing, challenges include the need for well-equipped infrastructure and specialised facilities, while complex regulations often lead to delays in approvals and commercialisation. A shortage of skilled professionals hinders growth, and securing funding for research and scaling production is challenging due to uncertainties. Protecting intellectual property faces issues with patent laws, while effective technology transfer is vital for translating research.

Maintaining consistent quality and adhering to global standards are other significant hurdles, especially for export products. Gaining market access and competing with established players pose challenges, particularly for newcomers. Public awareness and trust in biomanufactured products, notably in areas like genetically modified organisms, need focused efforts. Furthermore, amidst intense global competition, Indian companies must stay innovative to remain competitive.

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