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Review

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Pathways to Sustainable Biomanufacturing: Scalable Production of Biopharmaceutical Raw Materials and Biologics for Health Security

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How To Cite: Mariita, R.M.; Reedy, J.M.; Munga, H.G.; et al. Pathways to Sustainable Biomanufacturing: Scalable Production of Biopharmaceutical Raw Materials and Biologics for Health Security. *Global South & Sustainable Development* **2026**, *1*(1), 19. https://doi.org/10.53941/gssd.2026.100019

Received: 16 January 2026
Revised: 20 May 2026
Accepted: 8 June 2026
Published: 15 June 2026

Abstract: The increasing global demand for biopharmaceutical biologics, including vaccines, monoclonal antibodies, enzymes, cytokines, hormones and growth factors, is driven by aging populations, rising cancer incidences, the persistent threat of pandemics such as COVID-19 and endemic infectious diseases such as Tuberculosis and Malaria. While the global biologics market is projected to surpass $1 trillion by 2034, current centralized manufacturing models rely heavily on resource-intensive mammalian systems that pose significant economic and logistical barriers, particularly for the Global South. This review evaluates the imperative for adopting sustainable biomanufacturing pathways to enhance global health security and sovereignty. We critically assess diverse production platforms, ranging from traditional microbial and mammalian cell lines to emerging green systems such as transgenic plants, algae, and cell-free synthesis, against the Triple Bottom Line framework: environmental stewardship, economic viability, and social responsibility. The analysis highlights that while mammalian cells remain the industry standard for complex post-translational modifications (PTMs), plant-based and cell-free platforms offer scalability, reduced carbon footprints, and the potential for decentralized production. Furthermore, the integration of artificial intelligence (AI), digital twins, and single-use technologies is identified as a catalyst for optimizing yield and facilitating net-zero emissions targets. For the Global South, these approaches offer opportunities to overcome resource limitations through localized, low-input platforms. We conclude that transitioning toward resilient, localized, and eco-friendly biomanufacturing is essential to mitigate supply chain vulnerabilities, ensure equitable access to life-saving therapeutics, and safeguard populations against future biological threats.

Keywords: sustainable biomanufacturing; plant molecular farming; health security; pandemics; biologics scalability; security and sovereignty

1. Introduction

The global demand for biopharmaceutical biologics is on the uptick, driven by a variety of converging factors, including aging populations in developed countries, rising cancer incidences, and the persistent threat of pandemics

like COVID-19 [1–3]. Additionally, the burden of endemic infectious diseases is being compounded by antibiotic resistance, respiratory infections such as tuberculosis [4], and the emergence of personalized medicine modalities. An aging global population, projected to reach 2.1 billion individuals over 60 by 2050 [5], increases the prevalence of chronic conditions requiring biologics like monoclonal antibodies (mAbs) for Alzheimer's and cardiovascular diseases [6].

The global biologics market, valued at approximately USD 445.2 billion in 2024, is projected to surpass $1 trillion by 2034 [7,8]. This escalating demand is propelled by several converging drivers: shifting demographic factors such as an aging global population [5], epidemiological trends including rising cancer incidences and endemic infectious diseases [1], and the persistent threat of pandemics [9]. The impact of these drivers varies significantly by region. High-income countries predominantly require a robust biomanufacturing infrastructure [10] to address the expanding burdens of aging populations and chronic non-communicable diseases (NCDs), most notably Alzheimer's [6], oncology-related malignancies [11], and obesity [12–14]. Conversely, Low- and Middle-Income Countries (LMICs), predominantly in the Global South, contend with younger demographic profiles that are heavily impacted by endemic diseases and rapidly spreading outbreaks [15]. Addressing these dual, global pressures requires a paradigm shift away from fragile, centralized supply chains toward sustainable, resilient biomanufacturing governed by the Triple Bottom Line (TBL) framework.

1.1. Biopharmaceutical Types for Disease Treatment

Pharmaceutical biologics have been and continue to be a cornerstone for the management and treatment of many diseases. In particular, recombinant pharmaceutical biologics is a multibillion-dollar industry encompassing monoclonal antibodies [16], hormones such as insulin [17], growth factors such as growth hormones [18], therapeutic enzymes [19], among others. Additionally, Antibody Drug Conjugates (ADC), which consist of small molecule/toxin linked to mAbs that target surface receptor protein of cancerous cells, have been approved and are in use for cancer treatment [20].

Beyond full-length monoclonal antibodies, the single-chain variable fragment (scFv) has emerged as a critical class of biologics, particularly in the targeted treatment of B-cell disorders via chimeric antigen receptor (CAR) T-cell therapies [21,22]. Similarly, the bioengineering of recombinant insulin has revolutionized the long-term management of Type II diabetes, providing a scalable and safe biological solution for patients with advanced insulin resistance [23]. Moreover, the recent clinical success of glucagon-like peptide-1 (GLP-1) receptor agonists, the active ingredient in semaglutide, has revolutionized the treatment of Type 2 diabetes and chronic weight management [24]. Beyond metabolic regulation, recombinant biologics play a crucial role in human hormone therapy and genetic correction. For instance, recent advancements in gene therapy for Gaucher disease utilize viral vectors to restore enzymatic function, offering a curative alternative to lifelong enzyme replacement therapy [25].

Another development is the use of recombinant human growth factor (hGF), which has been used to treat children with growth hormone deficiency (GHD) [26,27].

Monoclonal antibodies are a major class of biopharmaceutical biologics used for the management and treatment of many diseases. Monoclonal antibodies are either under clinical trials or have been approved and used for treatment during outbreaks such as COVID-19 [28–30] Ebola [31–33], Zika [34,35] and control of endemic diseases such as malaria [36–38].

1.2. Use of Biologics to Fight Antibiotic-Resistance and Pandemics

The use of biologics for antibiotic-resistant respiratory infections, such as multi-drug-resistant tuberculosis (MDR-TB) [39,40], represents a rapidly evolving field that complements sustainable biomanufacturing efforts in addressing endemic and outbreak threats in the Global South. Unlike small-molecule antibiotics that directly target bacterial killing, biologics often function by boosting host immune responses through Host-Directed Therapies (HDTs) [40] or precisely targeting bacterial structures (e.g., via mAbs). Key modalities include mAbs, primarily by HDTs modulating inflammation (e.g., inhibiting IL-6 or TNF to prevent tissue damage) or enhancing bacterial clearance (e.g., targeting *M. tuberculosis* surface proteins) [41,42]; and cytokine therapies, using recombinant interferons (e.g., IFN-γ) to stimulate immune clearance [43].

While many biologics are used directly in clinical disease management, others serve auxiliary roles as critical raw materials for producing active pharmaceutical ingredients (APIs). A primary example is recombinant insulin; beyond its established role in diabetes metabolism, it functions as a vital growth factor in bioprocessing [44]. In large-scale mammalian cell culture, insulin is routinely supplemented in serum-free media to activate intracellular signaling pathways that stimulate cell division and biomass accumulation in vitro [45].

The market values of biologics and biopharmaceuticals, including vaccines, monoclonal antibodies, enzymes, growth factors, and recombinant proteins, are critical for global health security, enabling rapid responses to pandemics [46]. The biopharmaceutical sector is among the industries undergoing a transformative shift toward net-zero emissions, driven by the adoption of circular bioeconomy principles and energy-efficient bioprocessing [47]. Concurrent advances in distributed manufacturing have enabled the deployment of modular, resilient systems capable of operating in low-infrastructure environments [48]. These developments will benefit countries worldwide, particularly in the Global South, where limited domestic manufacturing and reliance on imports from multinational companies delay access to advanced biologics and increase household costs [49]. Sustainable, low-cost production platforms are therefore essential to improving health security and equity [50]. One way countries can harness biomanufacturing for biological threat preparedness and response is by enabling the rapid, decentralized development of medical countermeasures (MCMs), thereby reducing the typical timelines for product development, scale-up, and deployment of critical biologics [51–55].

1.3. The Triple Bottom Line of Biomanufacturing

By prioritizing rapid, localized production, these innovations will directly enhance health security and sovereignty, especially in the Global South, by shortening the distance between production and patient [56]. Creating robust pathways to sustainable biomanufacturing by using transgenic plants to produce animal-free, glycosylated biologics for gene therapy and cell culture will address vulnerabilities exposed by COVID-19, including supply chain failures and surging demand for equitable access [57]. Health security involves safeguarding populations against biological threats through resilient production systems [58]. This level of national health security preparedness can be objectively evaluated using multicriteria frameworks such as the Global Health Security Index (GHSI) and the Bulut Index-Beta (BI-β) method [59]. Furthermore, establishing decentralized biomanufacturing directly supports the capacity-building mandates outlined within the broader International Health Regulations (IHR) framework [60]. Sustainable biomanufacturing aligns with the Triple Bottom Line: environmental stewardship (e.g., low-carbon processes), economic viability (cost-effective scaling), and social responsibility (ethical, accessible production) [61,62].

Recent advances in 2024–2025 highlight biopharma's shift toward net-zero emissions and resilient manufacturing, enhancing health security through rapid, localized production. Major biopharmaceutical entities are advancing toward net-zero targets by 2030 through the adoption of smart manufacturing facilities that utilize IoT-enabled HVAC systems (smart ventilation) and integrate renewable energy, potentially cutting operational energy consumption by 20–40% [61]. Additionally, the rapid growth of biomanufacturing is placing pressure on policymakers to establish ethical norms across the sector; that ensure safe manufacturing, prevents the misuse of biological tools, align with societal needs, promote equitable distribution of benefits, and public trust [63].

The use of AI and new translational models are accelerating improvements in plant biology, crop breeding, and drug discovery [64,65], while single-use bioreactor suites (e.g., AGC's expansion in 2024 to 8 × 2000 L single-use bioreactors with two seed trains) double mammalian production capacity, bolstering resilience [66]. The integration of AI-driven 'Digital Twins' in bioprocessing allows for the real-time optimization of energy loads and media consumption, facilitating a transition toward carbon-neutral manufacturing without compromising yield [61]. An example of this is a recent digital twin application employed in a continuous chromatography process for monoclonal antibody (mAb) purification. This system leverages mechanistic modeling and online HPLC Process Analytical Technology (PAT) to make real-time pooling decisions, ensuring uniform charge variant composition and demonstrating a highly successful, automated control strategy [67].

While 60–70% of biopharma emissions can be abated at relatively low cost, the remaining 30–40%, particularly in Active Pharmaceutical Ingredient (API) manufacturing and deep-tier supply chains, face significant techno-economic barriers and high abatement costs, often exceeding $100 per metric ton of CO_2 [68]. Success in scaling these pathways requires more than biological innovation; it demands robust digital architecture. As a 2025 snapshot of biomanufacturing highlights, the transition to a sustainable bioeconomy is currently hindered by scalability and translational efficiency [10]. To overcome these barriers, adopting interdisciplinary research infrastructures (RIs) and meta-workflows is essential. These systems promote the interoperability, harmonization, and democratization of data, enabling a more equitable and resilient global production network that directly bolsters health security [10]. While recent reviews (2020–2025) focus heavily either on the technical limitations of emerging production platforms or on broad economic forecasts, this article uniquely bridges these domains. By applying a strict Triple Bottom Line (TBL) framework, we uniquely evaluate how green biomanufacturing platforms can enable localized, rapid-response health security.

The primary objectives of this review are to assess the demand drivers for biopharmaceutical biologics, such as aging populations, rising cancer incidences, pandemics like COVID-19, and emerging modalities, including cell and gene therapies, and to evaluate the imperative for sustainable pathways that bolster health security through resilient, eco-friendly production. It also aims to compare various production systems, encompassing microbial (e.g., bacteria like *Escherichia coli* and fungi such as *Pichia pastoris*), animal cells (e.g., CHO lines), insect cell lines (e.g., Sf9), plant-based platforms, animal-free biologics, cell-free approaches for rapid mRNA synthesis, egg-based methods for traditional vaccines, and algae systems like *Chlamydomonas reinhardtii*, while detailing their pros, cons, and alignment with the Triple Bottom Line of environmental stewardship, economic viability, and social responsibility. Furthermore, the review explores scalable pathways in biomanufacturing. Finally, it discusses implications for developing economies, including resource constraints and regulatory hurdles, as well as future innovations such as AI-driven optimization.

2. Public Health Imperatives and Demand Drivers for Biologics

The demand for biopharmaceutical biologics is driven by the rising prevalence of chronic conditions and emerging infectious threats, underscoring the need for sustainable manufacturing to enhance health security [69]. As the industry advances toward 2030, the strategic adoption of decentralized, green-biomanufacturing platforms is gaining priority [70], not solely to achieve ambitious net-zero emissions targets, but also to secure regional health sovereignty and enable rapid, agile response capabilities in resource-constrained environments.

Rising cancer incidences, with 19.3 million new cases in 2020, and expected to rise to 28.4 million by 2040 [71], drive demand for targeted therapies and immunotherapies, including animal-free vaccines and therapeutics [61]. Pandemics such as COVID-19, which caused over 7 million deaths, alongside outbreaks of Ebola, Zika, and Mpox, highlight the urgency of decentralized therapeutic production [72]. Emerging modalities, including cell and gene therapies (e.g., CAR-T for cancers), regenerative medicine, and organoid cultures for personalized treatments, further amplify demand, with the gene therapy market valued at $7.2 billion in 2023 and growing at a 19% Compound Annual Growth Rate (CAGR) [73].

These drivers evaluate the imperative for sustainable pathways that bolster health security through resilient, eco-friendly production. Traditional systems are vulnerable to supply chain disruptions, as seen in COVID-19 vaccine shortages, underscoring the need for decentralized, low-impact manufacturing [74]. Sustainable biomanufacturing pathways will reduce environmental footprints while ensuring rapid scalability, aligning with global public health resilience goals, including a 23% reduction in global warming and 25% reduction in particulate matter formation and ozone depletion compared to traditional manufacturing methods [75].

Diverse host systems offer pathways for biomanufacturing, each with implications for scalability and health security. Here, we compare them, detailing their pros and cons and their alignment with the Triple Bottom Line (TBL): environmental stewardship (e.g., low emissions), economic viability (e.g., cost-efficiency), and social responsibility (e.g., equity and safety).

Sustainable biomanufacturing of biologics has broad-ranging, global public health implications from infectious disease control to precision medicine to chronic disease management. Sustainable, scalable, and cost-effective approaches to biomanufacturing biologics and biosimilars for the treatment of endemic conditions, cancer, and other chronic diseases are a global public health imperative, though their importance varies by region, depending on health and system needs. Sustainable biomanufacturing also supplies the infrastructure necessary for rapid, tailored, and scalable treatment for infectious diseases, pandemic response, and medical countermeasures against biologic threats. Additionally, sustainable biomanufacturing provides a framework for improving global health equity and tailored responses by decentralizing design and large-scale manufacturing.

Chronic noncommunicable diseases (NCDs) and infectious disease outbreaks disproportionately impact Low- and LMICs, exacerbating global health disparities [76]. Rather than isolated epidemiological events, these compounding burdens highlight the severe logistical constraints of current centralized biomanufacturing. The reliance on vulnerable supply chains and resource-intensive facilities underscores the critical need for agile, decentralized production models capable of rapidly scaling biologics to meet shifting global health demands. While overall mortality is improving in some regions, morbidity and impact on disability-adjusted life years (DALYs) continue to remain a significant challenge. In the US alone, 90% of the $4.9 trillion (USD) annual healthcare expenditures are attributable to chronic conditions, while the global economic burden (direct costs and lost productivity) of chronic disease is projected to reach $47 trillion (USD) by 2030 [77,78].

In 2019, an estimated 704 million DALYs were attributed to infectious diseases (~85 pathogens), including *Staphylococcus aureus* and gram-negative bacteria such as *E. coli* and *Helicobacter pylori* [79]. A comprehensive review of disease burden from 1996 to 2023 found that influenza, Ebola, and Middle East respiratory syndrome-

related coronavirus (MERS-CoV) viruses were responsible for the highest outbreak rates, and Marburg and Ebola for the highest mortality rates [80]. A systematic review of 55 epidemiology studies from 1984 to 2021 found that airborne and droplet-borne infectious disease such as COVID-19, influenza, influenza A (H1N1), tuberculosis, norovirus, and severe acute respiratory syndrome (SARs) significantly contributed to overall mortality, morbidity, economic healthcare expenditure, and social impacts, while also increasing demand on strained supply chains and a reduced workforce [81]. The global cost of pandemics, such as COVID-19, is estimated to be nearly $570 billion annually (World Economic Forum). As with chronic disease burden, the global burden of infectious diseases is disproportionately higher in LMICs [79] While these estimates reflect the largest and most severe outbreaks, as global travel continues to increase, the spread and burden of infectious diseases will also rise [79,82].

Biologics and biosimilars are one method for addressing global chronic and infectious disease management and improving health equity at scale. Biologics are transforming the treatment of cancer, autoimmune disorders, diabetes, obesity, and other conditions, while biosimilar versions are making these solutions more affordable and sustainable, particularly in resource-constrained regions and LMICs [83]. As of 2023, the World Health Organization (WHO) recognized over 81 biologic and biosimilar therapies, representing 15% of all listed essential medicines, improving patient access to needed treatments [83]. Personalized biologics used in precision medicine also offer highly tailored treatments for cancer, genetic conditions, and autoimmune diseases by developing monoclonal antibodies, vaccines, and other cell therapies [84–86]. Synthetic biologics are being developed to enhance vaccine pathways, and biotechnologies are advancing health through large-scale impacts on food and nutrition, environmental waste, and economic and social justice infrastructure [87,88].

Global medical countermeasures (MCM) against biological threats, including bioterrorism and rapidly spreading pandemics, also receive substantial attention in high-income and post-developed countries, such as the US [89,90]. Global organizations dedicated to national and regional public health security enhance preparedness for biological threats by investing in infrastructure capable of rapidly producing tailored biologics at scale and on demand. This is largely achieved through sustainable, decentralized biomanufacturing efforts that can respond to regional needs using cost-effective methods [82,90]. Advanced manufacturing is a collective term for new medical product manufacturing technologies that can improve drug quality, address medicine shortages, and shorten time-to-market. Examples of some cross-cutting advanced manufacturing technologies include continuous manufacturing and 3D printing [91].

The sustainable biomanufacturing industry is rapidly expanding to address these large-scale concerns. The rapid expansion of biomanufacturing does not come without challenges and considerations. The pharmaceutical industry has a CAGR of 2.4%, yet only 0.2% products have undergone environmental impact studies [92]. Synthetic biologics for vaccine development in distributed biofoundries aim to decentralize manufacturing, bringing solutions closer to the identified threat and improving response time, affordability, and scalability, particularly for LMICs [88]. Sustainable biomanufacturing of biologics and biosimilars can also address economic, environmental, and social concerns, while providing global health security [92,93]. Global cross-sector partnerships and a Health in All policy (HiAP) approach are necessary for the scaled advancement of sustainable biomanufacturing for MCM, pandemic preparedness, and overall advancements in chronic disease management [86,94,95]. Decentralized, sustainable biomanufacturing models have demonstrated concrete success in LMICs. A premier example is the WHO mRNA Technology Transfer Hub established in South Africa, led by Afrigen Biologics. This initiative successfully developed AfriVac 2121 [96], providing a blueprint for how technology transfer and localized capacity building can circumvent intellectual property barriers and secure regional health sovereignty [97]. There has also been success in reducing the overall financial and health-system burden of the costly chronic autoimmune disease, rheumatoid arthritis, through sustainable biomanufacturing of biosimilar therapeutics [98].

3. Production Platforms for Pharmaceutical Biologics for Global Public Health

The production of recombinant biopharmaceutical biologics has relied on a diverse array of host systems, each offering distinct advantages and limitations in terms of scalability, post-translational modification capabilities, cost, and implications for global health security. These systems range from well-established traditional platforms to emerging non-conventional approaches that prioritize sustainability, decentralization, and resilience amid pandemics and supply chain disruptions.

Diverse host systems offer pathways for biologic production, each with implications for scalability and health security as described below.

3.1. Traditional Methods

3.1.1. Prokaryotic System

Bacterial cells are the primary prokaryotic expression system used to produce recombinant biologics. Bacteria, particularly *Escherichia coli*, remain a cornerstone of microbial biomanufacturing owing to their exceptionally rapid growth rates [99] (Figure 1), often doubling in as little as 20 minutes, enabling low-cost, high-volume production that is critical for rapid pandemic responses, including the prototyping and deployment of DNA-based vaccines [99,100]. This system's proven reliability is exemplified by its long-standing role in the commercial production of insulin and human growth factors (hGH) [101], proteins that do not require PTM, offering advantages such as minimal infrastructure requirements, high genetic tractability, and the absence of viral contamination risks, thereby supporting accelerated development cycles for emergency countermeasures against emerging infectious threats [101,102].

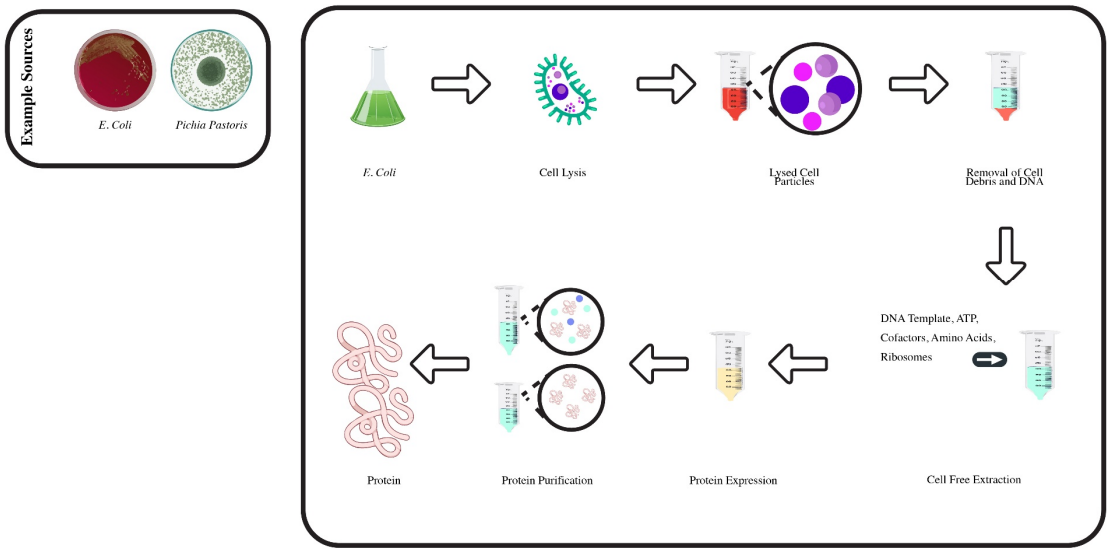

Figure 1. Schematic representation of the microbial biomanufacturing workflow for recombinant protein production utilizing *Escherichia coli* and fungal hosts (e.g., *P. pastoris*). Schematic illustrations and figures were created using Adobe Illustrator 2025 (Adobe Inc., San Jose, CA, USA). High-resolution scalable vector assets were obtained from Vecteezy (Eezy Inc., Bowling Green, KY, USA) and Freepik (Freepik Company S.L., Málaga, Spain) and subsequently modified to ensure scientific accuracy.

However, bacterial systems, such as *E. coli,* are fundamentally limited by the lack of eukaryotic post-translational modification (PTM) machinery (Table 1), which precludes critical processes such as glycosylation and proper disulfide bond formation, frequently resulting in misfolded [99], aggregated, or biologically inactive complex proteins [100]. This constraint is especially detrimental for glycosylated vaccines required during outbreaks, where the absence of human-like PTMs compromises immunogenicity, stability, and overall therapeutic efficacy [103]. Additionally, the presence of endotoxins (lipopolysaccharides) in the *E. coli* cell wall necessitates extensive and costly purification protocols to eliminate immunogenic risks and ensure clinical safety, thereby increasing downstream processing complexity and overall production costs [101].

3.1.2. Fungi Expression Systems

Fungal expression systems, such as *Pichia pastoris* and *Saccharomyces cerevisiae*, provide eukaryotic PTM capabilities, including glycosylation, and support high-density fermentation suitable for producing virus-like particles (VLPs) and monoclonal antibodies [102,104,105]. These systems offer cost-effective scalability and surge capacity, with recent advances in 2024 demonstrating the use of sustainable, chemically defined media that further enhance their environmental profile [106]. Nonetheless, fungal glycosylation patterns are often non-human (e.g., hyper-mannosylation), which can alter protein efficacy and immunogenicity, while proteolytic degradation remains a concern that may delay deployment during health crises [107].

3.1.3. Mammalian and Animal Cell Lines

Mammalian cell lines, particularly Chinese hamster ovary (CHO) cells, are the industry standard for producing complex biologics that require human-like PTMs, offering high-quality mAbs and vaccines with established regulatory approvals for pandemic applications [108,109]. These systems excel in scalability for monoclonal antibody production during health emergencies [110].

However, their high operational costs, slow doubling times, susceptibility to viral contamination, and dependence on expensive media significantly limit global equity and accessibility, particularly in resource-constrained settings such as the Global South [111].

3.1.4. Insect and Insect Cell Lines

Insect cell lines, such as Sf9 and Sf21, provide robust PTMs and are widely used with the baculovirus expression vector system for rapid production of VLPs and influenza vaccines [112,113]. These platforms are pathogen-free and effective for surge production during outbreaks [103]. Limitations include moderate scalability, dependence on viral vectors, and relatively high operational costs, which reduce resilience for large-scale, widespread health threats [114].

3.1.5. Eggs

Embryonated chicken eggs remain a traditional and cost-effective platform for seasonal influenza vaccine production, with a long history of supporting public health responses [115]. However, supply disruptions caused by avian influenza outbreaks, potential allergenicity, and slow adaptation to novel pathogens limit their utility in modern pandemic scenarios [116].

3.2. Non-Conventional Methods/Emerging Production Systems

3.2.1. Plants

Plants are increasingly used as platforms for producing vital biological molecules, such as pharmaceuticals and industrial biomaterials [117], through advanced strategies, including genetic engineering, process automation, and precision agriculture. As a result, plants now yield therapeutic proteins, including Elelyso (taliglucerase alfa) for Gaucher's disease [117,118], ZMapp for Ebola, seasonal influenza vaccines, and Covifenz (Medicago's plant-derived) for COVID-19 vaccine [117,119,120]. Plant-based expression systems, particularly seed-based platforms such as rice, wheat, tobacco, sorghum, etc., offer scalable, field-level production regarded as safe (GRAS) status, low-cost PTMs, and exceptional environmental advantages. Transgenic plant platforms can be ideal for cultivation on marginal lands and rapid pandemic response [121,122]. These systems enable decentralized, long-term stable storage of biologics and the production of animal-free, glycosylated therapeutics, significantly enhancing health security in resource-limited settings [70,123]. For instance, rice seeds have been engineered for production of high-yield human serum albumin (HSA), reaching 10.58% of total soluble protein [121,122], with enhanced yields via suppression of endogenous proteins [122]. Plant-based platforms can leverage innovations such as CRISPR/multiplex editing for enhanced yield. Specifically, the regulatory approach to transient Agrobacterium-mediated expression systems has streamlined the prototyping phase. Furthermore, using edible plant tissues as oral delivery vehicles offers a transformative translational pathway, potentially bypassing extensive downstream purification steps and eliminating cold-chain logistics entirely [124,125] (Figure 2). These advancements position plant molecular farming as a sustainable frontrunner, with applications extending to orphan drugs such as Repleva GAA, monoclonal antibodies for MPXV, and immunomodulatory proteins, thereby fostering equitable access and resilience against pandemics.

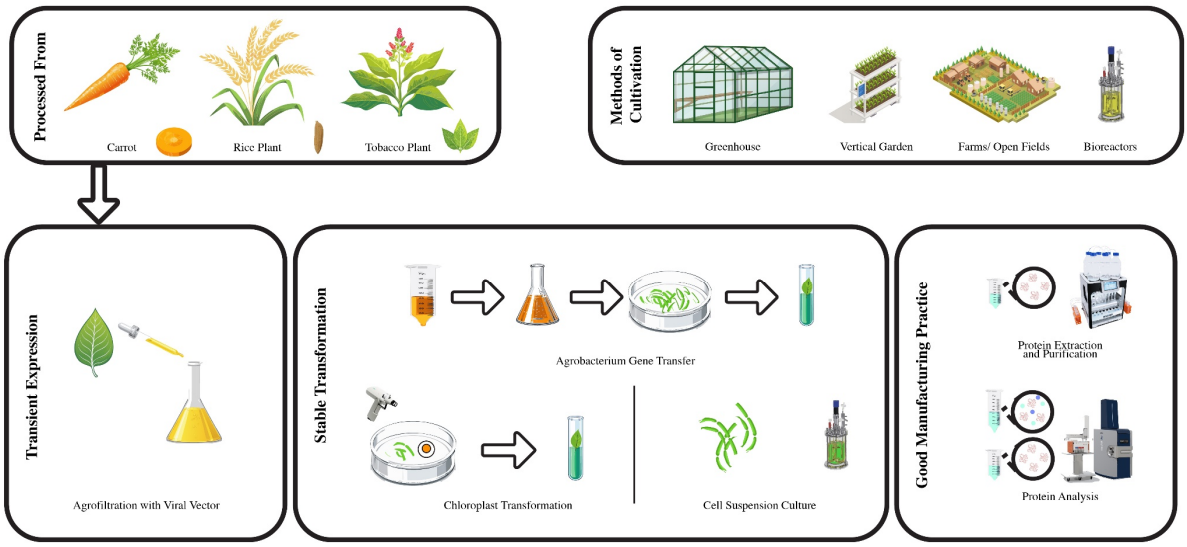

Figure 2. Interdisciplinary framework integrating plant molecular farming (PMF) and materials science for resilient vaccine production. Schematic illustrations and figures were created using Adobe Illustrator 2025 (Adobe Inc., San Jose, CA, USA). High-resolution scalable vector assets were obtained from Vecteezy (Eezy Inc., Bowling Green, KY, USA) and Freepik (Freepik Company S.L., Málaga, Spain) and subsequently modified to ensure scientific accuracy.

Despite these advantages, challenges persist, including extended timelines for transgenic development, plant-specific glycosylation patterns, and evolving regulatory frameworks. However, these limitations are increasingly mitigated through AI-driven genomic optimization and glyco-engineering [126]. Critically, seed-based platforms offer a strategic advantage by enabling ambient-temperature storage of recombinant proteins for extended periods without loss of bioactivity. This capability significantly reduces cold-chain dependency and enhances logistical resilience in resource-limited settings [121,127]. Consequently, plant-based expression systems represent a premier, cost-effective pathway for the large-scale production of biologics [101].

Drought-tolerant plant platforms can significantly enhance local production capacity in developing economies, addressing critical barriers such as limited investment, infrastructure constraints, and regulatory hurdles. By enabling cost-effective, regionally distributed manufacturing of animal-free biologics, this approach would promote health equity and resilience against endemic diseases and minimizes the impact of disruptions in vaccine coverage as seen during the COVID-19 pandemic [2].

3.2.2. Cell-Free Systems

Cell-free platforms enable ultra-rapid production of mRNA vaccines and other nucleic acid-based biologics with minimal infrastructure requirements, offering unmatched agility for pandemic response, as demonstrated by the swift development and deployment of mRNA vaccines during the COVID-19 crisis [57,106,128]. These systems utilize in vitro transcription and cell-free extracts to synthesize mRNA or proteins directly from genetic templates, thereby eliminating the need for cell culture scale-up, reducing contamination risks, and accelerating timelines from weeks to days [106,128]. This on-demand synthesis capability significantly boosts health security by enabling flexible, localized production in resource-limited settings and facilitating rapid adaptation to emerging pathogens [57].

Despite these advantages, cell-free systems face important limitations. High reagent costs, particularly for energy-regenerating components, ribosomes, and transcription factors, all pose substantial barriers to large-scale manufacturing and commercialization [129]. Moreover, current cell-free platforms have limited capacity to produce full-length, complex proteins with proper PTMs, limiting their utility to simpler biologics such as mRNA vaccines and short peptides rather than full-length mAbs or glycosylated therapeutics [124]. Additionally, dependency on lab-derived or commercially prepared components introduces supply chain vulnerabilities and further increases operational costs [128].

3.2.3. Algae and Moss Expression Systems

Green microalgae and Moss are photosynthetic eukaryotic organisms that have attracted interest as green host for production of recombinant proteins [130,131]. These relatively ‘simple’ life forms can easily be

transformed and cultivated in mineral solutions devoid of organic supplements making them more economically sustainable [132,133]. Additionally, their ability to carry out protein post-translational modification and efficient secretory pathways that facilitate straightforward downstream purification of recombinant proteins [130,134]. The PTM machinery can be exploited through genetic transformation of nuclear DNA. In contrast, the chloroplast is not equipped with all the eukaryotic PTM machinery like glycosylation [131]. Consequently, recombinant proteins that do not require glycosylation can be expressed in chloroplast. *Chlamydomonas reinhardtii* and *Physcomitrella patens* are the most widely used species of algae and moss respectively [132,135]. Both algae and moss are usually grown in bioreactors supplemented with light making them particularly attractive for the rapid and economical generation of vaccine antigens, including emerging pandemic-relevant targets such as SARS-CoV-2 spike protein domains [136], monoclonal antibodies [137,138]. The photosynthetic nature of algal systems supports sustainable, carbon-neutral bioprocessing and meets green manufacturing requirements.

Despite these advantages, algal platforms face significant limitations (Table 1), including substantially low yield and variability across different cultivation conditions, and dependence on light availability, which may restrict deployment flexibility and scalability across diverse geographic and industrial settings [130].

Table 1. Summary of production systems and their characteristics for biologics.

Organism	Cell Type	Organelle	Protein Assembly	Glycosylation	Cost (Initial/Operation)	Health Security Impact	References
Bacteria	N/A	N/A	None	None	Low/Low	Rapid prototyping; endotoxin risks	[99–102]
Fungi	N/A	N/A	Yes	Yes	Low/Low	Surge capacity; glycosylation issues	[102,106,107]
Animals	Cell	N/A	Yes	Yes	High/High	High quality; equity barriers	[110,111]
Insect	Cells	N/A	Yes	Yes	High/High	VLP speed; vector limits	[103,106,112]
Plants	Leaves/Seeds	Cytosol/Endosperm	Yes	Yes	Low/Low	Decentralized resilience; reg. hurdles	[70,121,122]
Cell-free	N/A	N/A	N/A	N/A	Low/High	Pandemic agility; scale challenges	[124,128]
Eggs	N/A	N/A	Yes	Yes	Low/Medium	Seasonal reliability; supply risks	[115,116]
Algae	N/A	Cytosol/Chloroplast	Yes	Yes/No	Low/Low	Eco-friendly; yield variability	[130,134,136]

4. Pathways to Sustainable Biomanufacturing

Biomanufacturing pathways are undergoing a profound evolution, transitioning from centralized, resource-intensive systems, such as large-scale mammalian cell fermentation facilities with high energy demands and vulnerability to supply chain disruptions, to decentralized, green alternatives that prioritize sustainability (Table 2), and accessibility to maximize Global Health impact [61,70]. To quantitatively evaluate sustainability trade-offs in bioprocessing, the application of Environmental Footprint (EF) and Life Cycle Assessment (LCA) methodologies is essential. These frameworks provide multi-category impact measurements, demonstrating measurable reductions in greenhouse gas emissions and water consumption when transitioning to green platforms. This paradigm shift is propelled by the integration of AI and synthetic biology, which are accelerating scalability through predictive modelling of genetic constructs, automated high-throughput screening, and precise genome editing, thereby optimizing expression vectors, enhancing protein folding efficiency, and boosting yields by up to several-fold in engineered hosts [126]. For protein-based biologics and conjugates, host selection pathways increasingly prioritize PTM fidelity and biosecurity, exemplified by endosperm-specific targeting in seed-based plant systems combined with RNA interference (RNAi) suppression of endogenous storage proteins (e.g., prolamins and glutelins), which creates dedicated deposition sites in protein bodies and achieves 3-fold or greater

yield improvements while ensuring proper glycosylation and acylation [121,122] (Figure 2). In contrast, nucleic acid-based biologics, such as mRNA therapeutics, derive substantial benefits from cell-free pathways that facilitate ultra-rapid in vitro transcription and assembly, slashing production timelines from weeks to hours and reducing costs by an order of magnitude compared to traditional cellular methods [57,128]. Environmental considerations unequivocally favor these green platforms, which exhibit inherently low water and energy footprints, while simultaneously sequestering carbon and minimizing waste outputs [70].

Table 2. Sustainability Matrix and Comparative Analysis of Biopharmaceutical Production Platforms based on Triple Bottom Line (TBL) Principles.

Platform	Sustainability Rating	Strengths	Limitations	Overall
Plants	★★★★★	Use sunlight, CO_2, and water as primary inputs. Scalable via agriculture or vertical farming. Strong alignment with the Triple Bottom Line.	Limited Regulatory Precedent, Longer development timelines, and plant-specific glycosylation.	Highly sustainable platform for Biomanufacturing.
Algae	★★★★★	Photosynthetic, carbon-negative Potential.	Limited Regulatory Precedent, Downstream Process is still developing	Exceptional sustainability with strong future potential
Bacteria	★★★★☆	Very fast growth with high yields, well-established and cost-efficient.	Limited PTMs. Endotoxin removal increases the downstream burden.	Highly sustainable for simple biologics.
Fungi/ Yeast	★★★★☆	Moderate energy inputs, robust fermentation at scale.	Glycosylation differences vs. Humans, still relies on fermentation infrastructure.	Broader capability than Bacteria, and relatively high sustainability scoring.
Insect Cells	★★★☆☆	Lower energy demand than mammalian cells, can be used in complex protein expression.	Viral Systems and regulatory and waste complexity, dependent on bioreactor infrastructure.	Moderately sustainable, Moreso than mammalian production.
Eggs	★★★☆☆	Established infrastructure (via vaccines). Moderate energy requirements.	Biosecurity concerns, limited scalability, and a larger ecological footprint	Moderately sustainable but constrained.
Animal Cells	★★☆☆☆	Industry standard for complex biologics. Human-like glycosylation.	Extremely energy and resource intensive. Significant Carbon Footprint.	Low Sustainability despite the quality of product output.

During emergencies and pandemics, plant-based systems promise to offer significant surge capacity through scalable cultivation and seeds that remain stable at ambient temperatures. This approach eliminates the need for cold-chain logistics and supports decentralized deployment, advancing health security in vulnerable regions, minimizing the impacts of geopolitical priorities. As a result, sustainable biomanufacturing is a critical strategy for building equitable and resilient global health infrastructure. The dynamics between protein complexity, production speed, and resource availability across different manufacturing pathways highlight the strategic advantages of green platforms for ensuring equitable access (Table 3).

Table 3. Summary of Suited Platforms for Specific Product Types.

Product Type	Examples	Best Suited Platform	Primary Rationale
Simple Proteins	Insulin, hGH	*E. coli*/Microbial	Fast doubling; low cost; no PTM needed
Complex mAbs	ZMapp, cancer mAbs	CHO or Plants	High PTM fidelity; PMF for low cost/scaling
Rapid Vaccines	mRNA (COVID-19)	Cell-free	Agility; days vs. weeks; low infrastructure
Orphan Enzymes	Taliglucerase alfa	Plant cell culture	Safety (animal-free); stable production
Antigens	SARS-CoV-2 spike	Algae/Moss	Eco-friendly; rapid generation; PTM capable

5. Conclusions and Future Outlook

The shift toward sustainable biomanufacturing is the most viable pathway to achieving global health security. While mammalian cell lines retain dominance for complex PTMs, their heavy resource requirements and infrastructure costs limit their resilience in decentralized settings. In contrast, plant-based and cell-free systems

demonstrate the strongest overall sustainability profiles, offering crucial advantages in surge capacity, ambient-temperature storage, and rapid response. The integration of AI-driven platforms and decentralized manufacturing pods will likely normalize 'Point-of-Need' biologic production by addressing existing supply chain vulnerabilities. Moving forward, practical research priorities must focus on overcoming current translational barriers. Specifically, significant investments in AI-driven metabolic modeling and a concerted effort toward regulatory harmonization for green host systems are required to fully realize the potential of these platforms. This represents a historic opportunity to achieve health sovereignty through innovation that prioritizes both planetary boundaries and equitable patient access.

Author Contributions

R.M.M.: conceptualization, methodology, software, original draft preparation, reviewing and editing; J.M.R.: methodology, original draft preparation, validation, reviewing and editing; H.G.M.: methodology, original draft preparation, validation, reviewing and editing; B.H.: methodology, software, visualization, original draft preparation, reviewing and editing. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

Acknowledgments

The authors express their sincere gratitude to the professors of SUNY Polytechnic Institute's MBA in Technology Management program. The intellectual rigor of the curriculum provided the foundational inspiration and strategic framework for this study.

Conflicts of Interest

J.M.R. and H.G.M. declare no conflict of interest. R.M.M. and B.H. are affiliated with CYCLYN Biosciences. CYCLYN Biosciences had no influence on the design or writing of the manuscript.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

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