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# Biomanufacturing as Key Technology for a Sustainable Bioeconomy

Roland Wohlgemuth*

*Abstract:* Scientific and technological advances have created new biomanufacturing opportunities by overcoming manufacturing challenges and problems in various industrial sectors step by step and thereby lead to sustainable value creation. Bottom-up biomanufacturing approaches can provide value to customers in a competitive environment and when located in a geographically well-connected ecosystem bring additional benefits, such as derisking of supply chains, reduction of complexity, or strategic autonomy. The strategic importance of biomanufacturing can also be seen by different top-down initiatives and platforms addressing common critical needs.

**Keywords**: Biobased raw materials · Bioeconomy · Biomanufacturing · Resource efficiency

***Roland Wohlgemuth*** studied chemistry and biology at the University of Basel, where he received his doctoral degree working on the structure and dynamics of phospholipid membranes with Prof. Dr. Joachim Seelig at the Biocentre of the University of Basel. He received a Swiss National Science Foundation Award and did postdoctoral work with Prof. Dr. Melvin Calvin at the Lawrence Berkeley Laboratory (LBL) and the University of California in Berkeley. He was employed by the US Department of Energy as a research scientist in artificial photosynthesis working with Melvin Calvin at the Lawrence Berkeley Laboratory (LBL) and the University of California in Berkeley. He then returned to Switzerland to lead the bioanalytical laboratories, to develop biochemistry/ biotechnology at Fluka, and to build research, development, and production laboratories for the biochemistry department. Fluka subsequently became part of the Sigma-Aldrich Corporation, which was acquired in 2015 by the Merck Group. Roland Wohlgemuth has been involved in national, bilateral, and European research projects, teaching biocatalysis and biotransformation courses and moved from industry to academia, working as a Professor at Lodz University of Technology. Roland Wohlgemuth is Member of the STRENDA commission and serves as President of the European Society of Applied Biocatalysis (ESAB) and the Swiss Coordination Committee for Biotechnology (SKB). He received the Biocat 2024 Lifetime Award.

## 1. Introduction

The annual economic value created by the services of the natural ecosystems has been estimated for the entire biosphere of planet earth to be of a similar order of magnitude as the global economy.[1–3] The natural ecosystems services provide not only a habitable planetary environment but also biobased and renewable resources for human utilization. These biobased and renewable resources include not only raw materials originating from biological carbon dioxide fixation, but also enzymes as nature's privileged catalysts or as starting points for novel biocatalysts with improved properties. In addition, these resources also provide principles of manufacturing, biocatalytic processes and pathways as nature's blueprints and starting points for developing resource-efficient biotransformations of raw materials to valuable bioproducts. In value creation from biobased resources the long experience in using bioprocesses and pathways for manufacturing has attracted increased global attention. This is especially important in view of the energy and material dependence on fossil resources and the actual planetary boundaries.[4,5]

Strategic risks in linear value chains can arise from waste accumulation from extractive and non-sustainable manufacturing technologies, fragility of long synthetic routes and complex supply chains, fluctuations in the raw materials' quality and availability, global storage levels and just-in-time production. The COVID-19 pandemic and other extraordinary crises, but also ordinary global shortages of certain products, have brought much attention to the world of manufacturing and to derisking the manufacturing of key products. Sustainable manufacturing technologies with shortened synthetic routes, simpler supply chains and circular value chains can reduce risks and provide opportunities for more resilient biomanufacturing routes to products from renewable resources. The transformation of linear extractive manufacturing systems to circular reconstructive manufacturing systems is therefore a future-oriented general approach for addressing planetary boundaries on an actionable level.

The conversion of biobased raw materials into useful products has been closely associated with the history of many human cultures over a long time and biomanufacturing can therefore benefit from the accumulation of a large and increasing amount of knowledge and experience.[6] Biomanufacturing activities have become highly relevant and create significant value for numerous economies, for example 438.8 billion dollars for US biomanufacturing in 2019.[7] The extraordinarily rich biodiversity, evolvability, renewability, and metabolic capacities of biological resources on planet earth thereby provide essential assets for manufacturing products. These starting points offer great opportunities for biomanufacturing, either by degradation of raw materials, or by synthesis, or by a combination of both, in a circular way analogous to bioprocesses in nature.

The extractive linear economy based on raw materials obtained from limited resources such as fossil and geological resources accumulate increasing amounts and types of waste associated with economic growth. Therefore an important task and

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*Correspondence:* Prof. Dr. R.Wohlgemuth, E-mail: roland.wohlgemuth@sk-biotechnologie.ch
SKB, CH-8021 Zurich, Switzerland; Lodz University of Technology, 90-924 Lodz, Poland, E-mail: roland.wohlgemuth.1@p.lodz.pl; ESAB, 1000 Brussels, Belgium; E-mail: roland.wohlgemuth@esabweb.org

endeavor of the 21st century is the rebalancing of the cycles and flows of elements which are relevant for life and are connected with planetary boundaries.[4,5] Biomanufacturing can contribute to this rebalancing towards a more sustainable bioeconomy by resource-efficient catalytic manufacturing processes utilizing renewable catalysts and raw materials (Fig. 1).

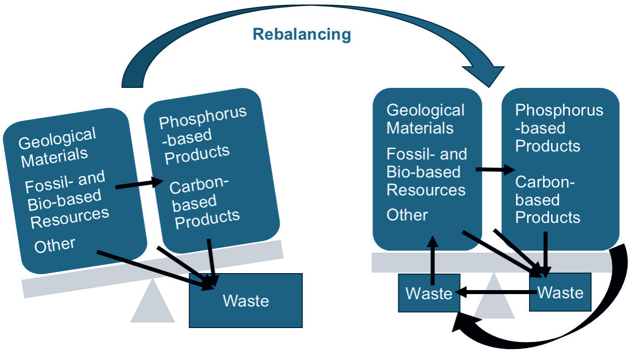


Fig. 1. The accumulation of carbon- and phosphorus-based products and its associated carbon- and phosphorus-containing waste leads to unbalanced phosphorus and carbon cycles. Rebalancing of the phosphorus and carbon cycles, which are relevant for life and connected with the planetary boundaries, is important and can be achieved by improved and novel resource-efficient bioprocesses leading to less waste, and a reutilization of carbon- and phosphorus-based products and its associated carbon- and phosphorus-containing waste.

The bioeconomy concept, which has been developed in Europe[8,9] and has been adopted worldwide, integrates the multidisciplinary approaches needed for transitioning non-sustainable extractive manufacturing to resource-efficient and sustainable biobased value creation architectures.[10,11] In view of limited resources and the complexity of these endeavors for a selected bioeconomy sector, its markets and beyond, a clear focus on what really matters as well as biomanufacturing using bioprocesses offer a way forward to support this transition by innovative process design and reengineering.[12,13]

Industrial biomanufacturing has been considered as the future of chemical production in the 21st century and beyond,[14] but successful biomanufacturing achievements have already been demonstrated by various industrial sectors in the past and present, for example in the production of metabolites, peptides, and proteins. Biocatalysis has become a crucial enabling technology for biomanufacturing, for significant advances in sustainable chemistry[15–17] and for designing new resource-efficient bioprocesses in various industrial sectors. These include new *in vitro* and *in vivo* biocatalytic reactions offering opportunities to expand the chemically accessible space.[18] The power of enzymes is also a great advantage for performing multi-step biocatalytic reactions and biocatalytic total synthesis.[19]

The dynamic and evolving nature of biomanufacturing is illustrated by the different set-ups in which biomanufacturing is involved in sustainable industrial manufacturing. Biomanufacturing activities range from completely biological processes using whole cells such as fermentation, cell culture, organoid production, biofabrication, to cell-free biocatalysis, the combination of fermentation and biocatalytic modification, and chemoenzymatic synthesis. This has made biomanufacturing attractive for the production of a widening spectrum of product groups, from small molecular weight product groups such as chemicals, metabolites, and natural products,[20–22] large molecular weight product groups like recombinant monoclonal antibodies, enzymes and other proteins, biopolymers, glycans, RNA and DNA,[23–26] to vaccines, whole cells and tissues.[27–29] Biologically functional higher level structures can be formed from these bioactive molecules, biopolymers, whole cells and tissues, by the use of various technologies such as bioassembly and 3D bioprinting, which is attracting significant attention in biofabrication.[30]

Biomanufacturing had already demonstrated its excellent performance and economic growth long before the COVID-19 pandemic. The timely availability and readiness of adequate infrastructure, a broad knowledge base and an experienced workforce for biomanufacturing have been absolutely key for overcoming the COVID-19 crisis. Biomanufacturing has been essential for the fast large-scale production of specific diagnostic tests, the antiviral drug Molnupiravir for the therapy of COVID-19 patients, and specific mRNA vaccines for preventing infections. Fragile supply chains and urgent biomanufacturing needs have also shown the importance of strategic autonomy for the production of highly important products.

Biomanufacturing is connected and interacting with an increasing number of industrial sectors, which can rapidly lead to new value chains and material flows. The blueprint of straightforward biotransformations in nature can also be of much interest to reduce the complexity of manufacturing processes, value chains and materials flows in several dimensions. Regional biomanufacturing ecosystems are therefore beneficial for such interactions, for simplified logistics and supply chains in a highly complex value creation architecture. Reducing the complexity of bioprocesses,[31] for example by having fewer reaction and purification steps, can lead to more robust biomanufacturing. Simplifying the overall time requirement from production to application is of great interest for on-demand biomanufacturing.[32]

## 2. Manufacturing Challenges as Opportunities for Biomanufacturing

Chemical total synthesis has been highly successful in designing the first synthetic route to the most complex natural products, contributing to the correct structural identity of the natural product extracted and purified from biological sources and over coming analytical and preparative challenges. Manufacturing challenges such as non-sustainable production processes with low efficiency can lead to high production costs of natural products made by chemical total synthesis as well as by extraction from biological resources (Fig. 2). Alternative synthetic routes can also become attractive in the case of scalability issues when a viable industrial manufacturing process for complex natural products needs to be developed to meet increasing demands. Although efficient manufacturing processes starting from biobased raw materials instead of fossil resources are desirable and attractive with respect to sustainability, carbon dioxide emissions, and biogenic carbon benefits, various manufacturing challenges may occur (Fig. 2).

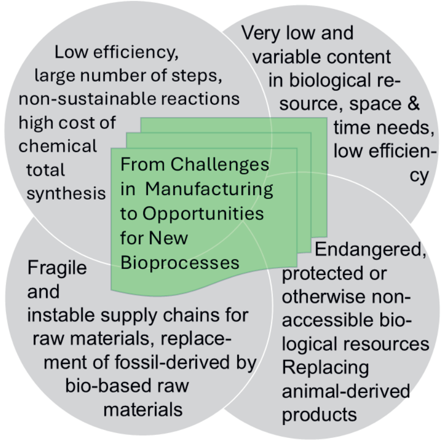
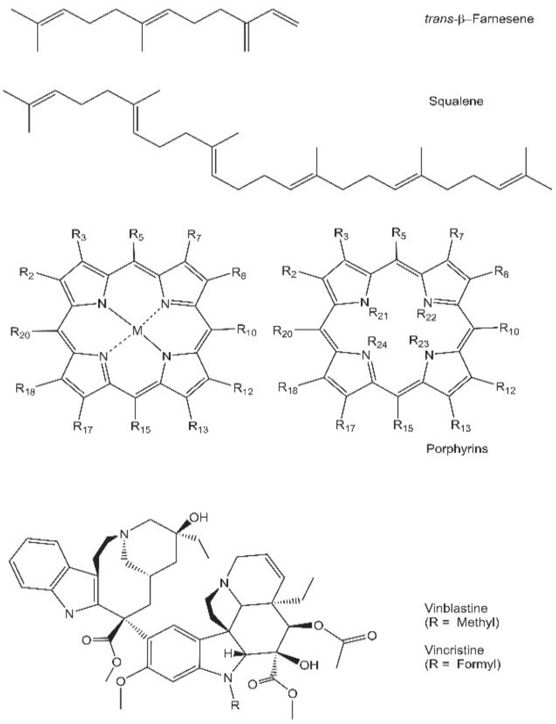


Fig. 2. Selected potential manufacturing challenges which may arise in chemical synthesis as well as in production from biological resources.

The isolation and purification of a natural target compound occurring in very low and variable percentages in a biological resource relate to extensive and challenging work, which may be a limiting factor (Fig. 2). Manufacturing the required quantities of a natural target compound, or its precursors, from plants may be limited by the space of the required land resources and the corresponding time needed for growing the plants. Therefore, the development of biomanufacturing processes is an attractive approach to overcome challenges and limitations in biological and chemical manufacturing processes or combinations thereof towards target compounds. (see Scheme 1 for some examples).

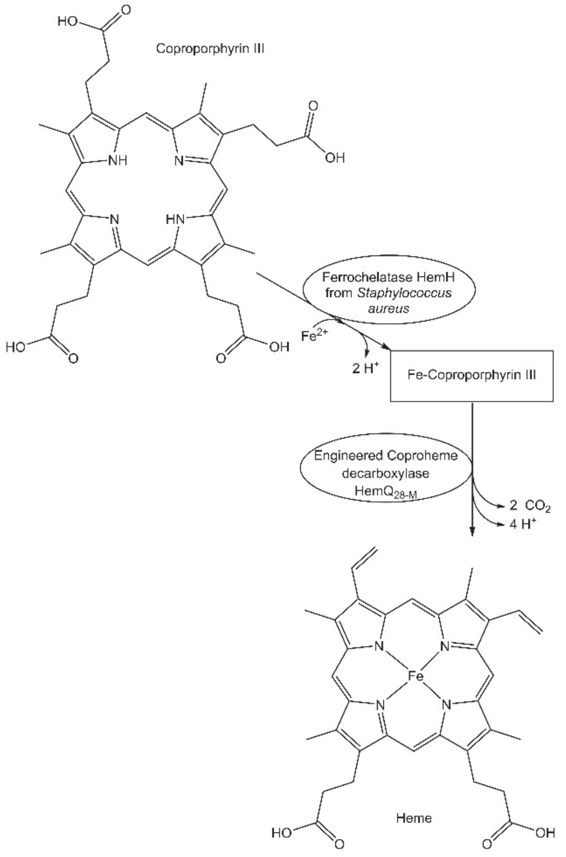


Scheme 1. Selected target compounds for which manufacturing challenges have been opportunities for biomanufacturing.

A significant fraction of the approved therapeutic compounds of small molecular weight for the treatment of human diseases and numerous other products with key functions are derived from natural products.[33] Therefore, the characterization and reconstitution of the involved biosynthetic pathway enzymes is not only a fertile ground for the discovery of novel enzymes, but also opens up opportunities for the development of new biomanufacturing processes.

Major challenges exist in the efficient production of porphyrins, such as inefficient and non-sustainable isolation and purification processes from animal or plant sources, and high costs for chemical total synthesis or semi-synthesis. It is therefore of much interest to develop new approaches and strategies to produce various porphyrins by highly efficient bioprocesses. The extracellular free coproporphyrin III (starting material in Scheme 2), a key intermediate in a bacterial heme biosynthetic pathway, has been produced at a concentration of 16.5 g $L^{-1}$ at the 5 L scale, and at the higher concentration of 19.6 g $L^{-1}$ at the 200 L scale through improved supply of dissolved oxygen, by fed-batch fermentation of an engineered and optimized *Rhodobacter sphaeroides* HY01 strain.[34] Genome-wide CRISPR interference screening was essential for the identification of a bottleneck in free coproporphyrin III overproduction. This enabled the discovery that inhibiting the transcription of the *hemN* gene, which encodes coproporphyrinogen III oxidase, prevents the consumption of the precursor and is thus favorable for the formation coproporphyrin III.[34] Ferrochelatase HemH from *Staphylococcus aureus* catalyzed efficiently the reaction of coproporphyrin III with various metal ions, such as $Fe^{2+}$, $Co^{2+}$, $Mn^{2+}$, $Cu^{2+}$ and $Zn^{2+}$, to the corresponding specific metallo-coproporphyrins III, thereby reaching complete conversions.[34]

A highly active coproheme decarboxylase HemQ, which was obtained from screening HemQ homologues and evolving coproheme decarboxylase from *Alicyclobacillus sacchari*, was used together with Ferrochelatase HemH from *Staphylococcus aureus* to catalyze the two-step biocatalytic reaction of coproporphyrin III and $Fe^{2+}$ to heme (Scheme 2), reaching 75% conversion.[34]



Scheme 2. Two-step biocatalytic reaction of coproporphyrin III and $Fe^{2+}$ to heme.

The worldwide supply of the essential anti-cancer drugs vinblastine and vincristine depends on their production from natural biological resources in low yields.[35] In addition, the yields after the purification of extracts from dried leaves of the plant *Catharanthus roseus* can vary depending on environmental conditions.[35] Although pioneering investigations of the chemical total synthesis of these complex monoterpene indole alkaloid structures build on multiple reaction steps and interesting precursor couplings,[36] their translation into a viable chemical production process at an industrial large scale is challenging. Therefore, a milestone has been achieved with the optimized expression in yeast of all the genes in the biosynthetic pathways of the vinblastine building blocks vindoline and catharanthine, and the demonstration of the biocatalytic multi-step synthesis of vindoline and catharanthine by highly engineered yeast cells.[35] Vinblastine was then prepared by a chemical coupling procedure of vindoline and catharanthine, which were obtained after isolation from the corresponding fermentation broths and purification.[35]

Further manufacturing challenges can result from fragile and instable supply chains, or from declining, endangered, protected or otherwise non-accessible biological resources being the natural product origin (Fig. 2). Thereby, also new chemoenzymatic routes starting from abundant and easily accessible biobased raw materials are attractive, such as *trans*-β-farnesene, which is commercially manufactured by engineered yeast strain fermentation at an industrial large scale.[37] Starting from biobased *trans*-β-farnesene more sustainable chemoenzymatic routes have been developed in order to overcome manufacturing challenges for plant-derived products such as the fragrance (-)-ambrox,[38] as well as for animal-derived products, such as squalene from shark liver oil, which is used as a vaccine adjuvant.[39]

## 3. From Scientific and Technological Advances to Industrial Biomanufacturing

The production of paclitaxel, a generic name for an important anticancer drug marketed under the brand name taxol® among others, has been achieved by extraction from *Taxus* species and other sources, by various chemical and biological production methods, each having its advantages and disadvantages.[40,41] Chemical total synthesis routes to taxol® represent a milestone and also provides numerous analogues of taxol®.[42–44] However, the costly and lengthy syntheses with low overall yields are not suitable for industrial production.[43,44] Direct isolation from slowly growing *Taxus* trees is a non-sustainable and not an economically feasible production method, as the paclitaxel content is extremely low and variable, and some *Taxus* plants are endangered and rare.[42] Industrial scale production of taxol® has been achieved by semi-synthesis starting from the key intermediates 10-deacetyl-baccatin III and baccatin III, which are obtained from the cultivation of *Taxus* plants.[40,41,45] Nevertheless further progress towards a fully enzymatic biomanufacturing route is of much interest, but requires the identification of the whole biosynthetic pathway and its regulation. The characterization and reconstitution of the enzymes in the biosynthetic pathway to baccatin III is a great opportunity for the further development of a short and sustainable biocatalytic route towards baccatin III and the important anti-cancer drug paclitaxel.[45]

Biomanufacturing also plays an important role in the production of some vitamins, where development of new routes and improved processes towards the use of renewable starting materials and catalytic instead of stoichiometric reactions is continuing.[46,47] The characterization of anaerobic and aerobic pathways for the microbial biosynthesis of vitamin $B_{12}$ and advances in understanding all of the enzymes involved have enabled the development of fermentation processes, which are now at the heart of the industrial large scale production of vitamin $B_{12}$ worldwide.[48,49] This was due to the industrial advantages and high step economy of vitamin $B_{12}$ biomanufacturing versus the milestone achievement of chemical total synthesis, requiring a much larger number of synthetic reaction steps.[50,51] Further research and development, for example towards higher space-time yields, novel enzymes and systems, and continuous process improvements are however still desirable and are of much strategic interest.[52]

Design-build-test-learn cycles have been very successful in rapid prototyping new biomanufacturing routes to target products and improving their titers in an iterative way.[53,54] As development time is not only key when a critical need for an intermediate or a target product arises but also in the selection of new biomanufacturing processes, it is essential to have a realistic evaluation of the time required to get an initial production system up and running for a biomanufacturing process. This task was realized by developing, within a first phase of 3 months, initial production systems for 10 target compounds, which included chemicals with and without known biological routes as well as plant natural products lacking biosynthetic enzyme information.[55] Out of the 10 molecules, six of the desired molecules or a closely related one could be produced with initial titers of up to 238 mg/L within 3 months, requiring a diversity of approaches in a centralized facility.[55] Advances have been made in developing initial production systems for the 4 other target compounds and design gaps have been identified.[55]

From rapid prototyping of new bioprocesses[56,57] to their scaling to industrial biomanufacturing, advances in the molecular and engineering sciences are of utmost importance towards the development of a viable route for the production of the target product.[58,59] Finding a suitable balance between different requirements and keeping the final goal in mind are important for moving to full-scale manufacturing.[60] This is also essential for over coming various limitations regarding scientific, technological and economic aspects, such as concentration, space-time yield, downstream processing, recovery and purification of the target product,[61,62] capacities, feedstock supply, infrastructure, and production costs.[63–65] Bioindustrial manufacturing readiness levels (BioMRLs) have been suggested for a generalized description of the maturity of a biomanufacturing process.[66] The interconnections between the scientific and technological advances, from discovery through different generations of products, and different types of industrial biomanufacturing are illustrated in Fig. 3 by the significance of biomanufacturing in the production of different generations of statins.[67] Microbial fermentation has been used for producing a first generation of statins (Fig. 3), while their derivatives have been produced by a combination of microbial fermentation with bioconversion.[67] The introduction of biocatalytic reaction steps into a chemoenzymatic route has been of crucial importance for stereoselectively producing better statins (Fig. 3) with improved properties.[67]

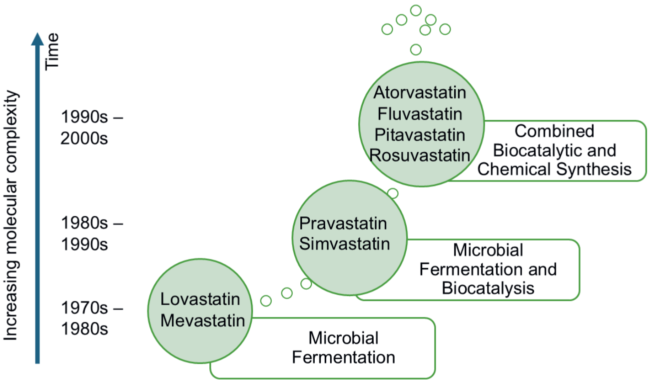


Fig. 3. Significance of different types of industrial biomanufacturing for the production of natural, nature-derived and synthetic statins.

Taking inspiration from nature, great advances have been achieved in the use of phosphorus in its oxidation state of +5 for sustainable biocatalytic manufacturing of oligonucleotides, DNA and RNA.[68–70] The tremendous improvements which have been achieved for the biocatalytic synthesis of DNA through 32 rounds of directed evolution have made the terminal deoxynucleotidyl transferase TdT-33 a prototype enzyme for preparing DNA with higher efficiency, quality and sustainability than traditional phosphoramidite chemistry.[71] Using 3'-phosphate-blocked 2'-deoxynucleoside triphosphates as reversible terminators for polymerization control, the efficiency of incorporation was increased 200-fold to > 99% with the engineered TdT-33 at a more than 600-fold reduced extension time of 90 s.[71] The impressive and robust performance of variant TdT-33 represents a major achievement for the biocatalytic synthesis of high-purity DNA at a commercial scale.[71]

Advances in DNA-template-based polymerization of natural and modified nucleotides catalyzed by RNA-polymerase and breakthrough discoveries on the translation efficiency and non-immunogenicity of mRNA with modified uridines and their delivery have enabled the development of mRNA vaccines.[72,73] Fast and global biomanufacturing of the SARS-CoV-2 mRNA vaccines at industrial large scale was critical for saving human lives and overcoming the COVID-19 pandemic.[74]

## 4. Biomanufacturing Initiatives

The strategic importance of biomanufacturing for a fundamental transformation in the 21st century and for addressing critical needs in robust supply and sustainable value chains is clearly demonstrated. A number of initiatives and platforms dealing with biomanufacturing have been created in several countries, not only from academic, industrial and non-governmental organizations but also from governments.

The White House issued on 12 September 2022 the executive order 14081 of the President of the United States on 'Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy'.[75] Biomanufacturing refers to the use of biological systems for developing products, tools, and processes at a commercial scale.[75] The corresponding efforts have been referred to as the 'National Biotechnology and Biomanufacturing Initiative', and the policy was an approach involving the whole government and coordinated by the administration.[75] As a result, the White House released on 15 November 2024 a report of the Biomanufacturing Interagency Working Group, creating a roadmap for a national biomanufacturing ecosystem.[76] In December 2022 the Executive Office of the President of the United States published the report on 'Biomanufacturing to Advance the Bioeconomy' by the President's Council of Advisors on Science and Technology, co-chaired by Frances H. Arnold, Maria T. Zuber, Arati Prabhakar and Francis Collins.[77] An analysis of the gaps and opportunities for biomanufacturing in the U.S. recommends "*to invest in the science of biomanufacturing, to invigorate a national innovation pipeline for advanced biomanufacturing, and to create financial incentives for investments into biomanufacturing*".[78] The executive order 14081 of 12 September 2022 on 'Advancing Biotechnology and Biomanufacturing Innovation for a Sustainable, Safe, and Secure American Bioeconomy' was however revoked on 14 March 2025 by the 47th President of the United States.

The National Security Commission on Emerging Biotechnology (NSCEB) delivered on the 8th April 2025 the report on 'Charting the Future of Biotechnology' containing an action plan with 49 recommendations to the U.S. Congress (see https://www.biotech.senate.gov/press-releases/nsceb-publishes-final-report/).

In China, with its rich bioresources and large market, biomanufacturing is among the four major areas of strategic priority in the two-stage bioeconomy development plan 2021–2035.[79] Biomanufacturing was mentioned among the future industries for which the establishment of a mechanism for investment growth and cultivation was described as a task in the 2025 Government Work Report by the Chinese Government.[80] Significant attention is given to the biomanufacturing industry in China, as described by the Ministry of Industry and Information Technology (MIIT).[81]

The EU Commission has mentioned biomanufacturing in the communication on 20 March 2024 as one of this century's most promising technology areas towards achieving numerous goals and for modernizing its industrial and primary sectors.[82] The EU Commission considers biomanufacturing as an important technology area for enabling bioeconomy at large, by increasing circularity and decreasing dependence on fossil-based raw materials, enhancing an open strategic autonomy and resilience.[82] Based on the identified challenges and opportunities, the EU Commission has communicated to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions a way forward for biomanufacturing in the EU.[82]

The ambitious new biomanufacturing initiative, which India has launched with the new program BioE3, an abbreviation for Biotechnology for Economy, Environment and Employment, aligns with national priorities and the vision to become a developed country by 2047.[83] The Indian bio-manufacturing initiative, which was approved by the Union Cabinet on 24th August 2024, aims at fostering high-performance biomanufacturing by setting up domestic biomanufacturing capabilities and facilities, developing workforce skills and accelerating the transition to biomanufacturing.[84] The implementation plan of BioE3 was published in January 2025 and includes the thematic areas of biobased chemicals and enzymes, functional foods and smart proteins, precision therapeutics, climate resilient agriculture, carbon capture and utilization, and futuristic marine and space research.[84] The government of India aims at making India a global biomanufacturing hub.[85]

The Japanese government has been developing since 2019 the Japan Bioeconomy Strategy to realize the most advanced bioeconomy society in the world by the year 2030, this was revised on June 3, 2024 to become an integrated innovation strategy,[86] the Bioeconomy Strategy.[87] A large budget of 1 trillion Yen is allocated to biomanufacturing and other bioeconomy areas, building on strengths such as abundance of biological and genetic resources, culture and fermentation technologies, capabilities for drug discovery and high-quality crop development.[87] The biomanufacturing area of the Green Technologies of Excellence (GTeX) Program aims at creating a system infrastructure for next-generation biomanufacturing and at applying biomanufacturing technologies to a broad range of manufacturing industries.[88]

## 5. Conclusions and Outlook

Scientific and technological advances in industrial biomanufacturing of numerous products and materials have not only enabled the improvement in the quality of human life but also provided tools and methods for addressing the many old and new, small and big manufacturing challenges. System thinking is thereby useful for reducing manufacturing complexity, creating new value chains and improving resource efficiency. Regional biomanufacturing ecosystems in a small country like Switzerland can facilitate such interactions, simplify logistics and supply chains in a highly complex value creation architecture. The biomanufacturing field is developing in a highly dynamic way and supported by various initiatives worldwide. New approaches such as the use of cell-free biomanufacturing,[89,90] cultured meat production[91] and on-demand biomanufacturing of sensitive products like conjugate vaccines[92] look very promising. The mutually beneficial close connection of innovation with biomanufacturing is highly important for Switzerland. Working together towards a strategy for the further development of biomanufacturing in Switzerland will not only be valuable for the highly diversified national ecosystem but also towards its highly connected European and global context. Long-term commitment is therefore key for developing and maintaining state-of the-art infrastructure, generating, and standardizing a broad knowledge base, educating, and inspiring people to contribute their work to biomanufacturing.

Biomanufacturing is also being considered for missions with increasing duration and distance from the planet earth in the exploration of space.[93] For the quality of life on planet earth, biomanufacturing represents a path forward to act and change on our planet the way things are manufactured and consumed worldwide. The many biomanufacturing initiatives demonstrate global thinking and national/regional actions. The transition to a sustainable bioeconomy offers new biomanufacturing opportunities in various areas and contexts. The ancient natural cycle of sowing, maintaining, growing, and harvesting, which enabled the great transition to human settlements is also important in a broad sense for biomanufacturing. Long-term and stable funding of investments, maintenance of adequate infrastructure, research, development, and innovation, for a broad knowledge base and education of an experienced workforce for biomanufacturing, can provide an agile and resilient biomanufacturing ecosystem.

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