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Way Forward for Biomanufacturing and Biotechnology in Europe

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Abstract: To restrict global warming to a maximum of 1.5 °C, greenhouse gas emissions need to be reduced to 'net zero' by 2050. The transition from the current, largely fossil-based global economy towards a circular, no-waste (bio-) economy based on renewable raw materials is seen as a critical pillar. In this paper, we explore the sustainability benefits as well as the implementation opportunities and challenges in Europe for three biomanufactured products used in animal and human nutrition, *i.e.* vitamins A and B_2 and canthaxanthin. To allow the biomanufacturing industry to leverage its full potential and to achieve 'net zero' in time, it will be crucial for European policy makers to create the appropriate framework conditions for incentivizing the required transformation of the chemical sector as well as for securing the competitiveness of European industry.

Keywords: Bioeconomy · Biomanufacturing · Ecological footprint · Life cycle assessment · Sustainable sourcing · Vitamins

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1. Introduction

dsm-firmenich was created in 2023 through the merger of two iconic companies: Firmenich and DSM (Dutch State Mines), founded in Switzerland in 1895 and in the Netherlands in 1902, respectively. The two legacy companies underwent multiple transformations and have grown to become global leaders in their respective fields. The combined company, dsm-firmenich, is now an innovation powerhouse in nutrition, health, and beauty with sustainability at the heart of who it is and how it operates.

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dsm-firmenich looks back at a rich history in biomanufacturing. The 'Nederlandsche Gist- & Spiritusfabriek' (Dutch Yeast and Ethanol Factory) was founded in Delft in 1869 and acquired (as Gist-brocades) by DSM in 1998.[1] It began with the production of yeast for baking bread. In World War II, the company started secretly to develop a production process for penicillin using a fungus from the *Penicillium* genus. Fermentative and/or biocatalytic production was later expanded to other antibiotics and food, feed and industrial enzymes.[2] At Hoffmann-La Roche (the Roche Vitamins division was acquired in 2003 by DSM), a microbial oxidation step had been used since the 1930s to produce vitamin C.[3] This process was used for approximately 80 years but has since been fully replaced globally by fermentative production of an intermediate, 2-ketogulonic acid, which is then chemically converted to vitamin C. Later, through internal developments, acquisitions and the merger with Firmenich, fermentative and/or biocatalytic production was expanded to a myriad of other products, in the areas of vitamins (*e.g.* vitamin B_2[4]), colorants (*e.g.* carotenoids[5]), dairy cultures, omega-3 fatty acids,[6] human milk oligosaccharides,[7] and flavours and fragrances.[8]

The Earth is currently facing multiple and intricately intertwined global crises such as: (i) global warming due to the burning of fossil fuels, deforestation and industrial processes; (ii) rapid loss of plant and animal biodiversity due to human activities such as habitat destruction, pollution and overexploitation; (iii) water scarcity due to increased frequency of droughts, melting glaciers and snowpacks, rising sea levels, extreme weather events, and increased evaporation; and (iv) hunger and malnutrition due to poverty, political conflicts, climate change, socioeconomic inequality between developed and developing countries, and the associated uneven distribution of food.

To overcome these global challenges and secure a viable planet for future generations while promoting health and social prosperity, fundamental changes are necessary; these are crucial for achieving the targets of the Paris Agreement on climate change[9] and the European Green Deal,[10] as well as the net-zero ambition by 2050 as postulated by the United Nations Net-Zero Coalition (https://www.un.org/en/climatechange/net-zero-coalition). The use of fossil energy sources such as natural gas or coal for heat supply and electricity in combined heat and power plants (CHP) for industrial manufacturing are major contributors to global warming. Achieving net-zero greenhouse gas (GHG) emissions requires not only switching to renewable energy sources but also 'de-fossilizing' the raw material base by increasing the use of bio-based or CO_2-derived raw materials and/or waste streams.[11]

Biotechnology and biomanufacturing can play a pivotal role in this transformation. Modern biotechnology relies on precision fermentation – using microorganisms (such as bacteria, yeast, filamentous fungi, or microalgae) – or biocatalytic processes using tailored enzymes to generate industrial products from renewable starting materials. Modern biotechnology can be used to make products in multiple industries including food and feed.

To achieve the required transformation, innovation will be crucial and will require both public and private commitment and financial investment. The public commitment is underscored by the EU's ambition to boost biotechnology and biomanufacturing[12] as well as by the proposed new EU Biotech Act which will likely be published in 2026. To attract private investment and thereby promote innovation, appropriate framework conditions are key. Firstly, proportionate regulatory frameworks are essential to guarantee a timely market introduction of innovative products. Secondly, supporting market demand through public procurement policies, consumer information, or nudging can drive adoption. Thirdly, securing access to sufficient, cost-competitive, and sustainable energy and raw materials is crucial for production. Additionally, creating effective incentives such as tax benefits, subsidies, or investment aids will support the desired transition. Finally, academic research funding under Horizon Europe should be prioritized to stimulate breakthrough innovation to address the key challenges for the required transformation.

The purpose of this article is to emphasize dsm-firmenich's commitment to bio-innovation and biomanufacturing in Europe, by featuring three examples of feed and/or food products developed and/or implemented over the past 35 years: vitamin B_2, which has been biomanufactured for more than two decades; canthaxanthin, which has been introduced very recently; and vitamin A, which may become a game changer in sustainable biomanufacturing. We will also provide a glimpse at the sustainability benefits of these examples and will use them to highlight some key challenges and policy needs for biotechnology and biomanufacturing in Europe.

2. Vitamin B_2 – Economic and Sustainability Benefits Go Hand in Hand

Vitamin B_2 (riboflavin) is a water-soluble vitamin that is an essential coenzyme for redox reactions in many different metabolic pathways. Vitamin B_2 is synthesized naturally by plants and by numerous microorganisms; on the other hand, animals depend on nutritional sources, including contributions from the intestinal microbiota. Accordingly, 70–80% of the industrially produced vitamin B_2 is used as a feed additive, whereas 20–30% is used as food additive and for pharmaceutical applications.[4]

Vitamin B_2 was first synthesized by Hoffmann-La Roche in the 1930s. For nearly five decades, the vast majority of vitamin B_2 was produced chemically. In 1990, BASF started up vitamin B_2 production using a genetically engineered fungus, *Eremothecium gossypii (*formerly called *Ashbya gossypii*), and phased out chemical production six years later.[13] In 2000, Roche Vitamins switched from chemical to biotechnological production, using a genetically engineered bacterium, *Bacillus subtilis*.[14] Investment costs at the time were 110 Mio. Swiss francs. Today, virtually all vitamin B_2 globally is produced using genetically engineered microorganisms in precision fermentation.

Both BASF and Roche Vitamins (now dsm-firmenich) emphasized the sustainability benefits of biotechnological over chemical production of vitamin B_2. For the biotechnological process, comprehensive eco-efficiency analysis by BASF (undertaken in 2003) revealed a 30% decrease in CO_2 emissions, a reduction in hazardous substances, a 25% reduction in energy consumption and a 50% reduction in material consumption.[13] This was accompanied by a 40% reduction in production costs. When Roche made its switch, the previous chemical production process – comprising 7 reaction steps and using 12 raw materials plus 7 solvents – was replaced by a simple, one-step fermentation process, in which sugar is converted into vitamin B_2. The use of fossil raw materials was reduced by 75%, wastewater by 67%, and exhaust air by 50%.[15] It is these compelling economic and environmental benefits that triggered the complete shift from mostly chemical to exclusively biotechnological production in a period of only approximately 15 years.

It is imperative to continue to strive for further improvements in both the production strain and the process, using state-of-the art technology, for instance genome editing, advanced analytics, or computer modelling. This will require highly skilled researchers that are at the forefront of the technological developments. Furthermore, dsm-firmenich's vitamin B_2 factory in Grenzach, Germany, is an advanced biomanufacturing facility, containing around 6000 I/O devices (input/output; *e.g.* valves, sensors, controllers), which enables the plant to be operated in a highly automated manner by a relatively small team of operators. Again, to run such a production asset in a reliable and efficient manner, a highly skilled workforce is required, further contributing to an attractive job market in the European life sciences sector.

Safety is an integral consideration for sustainability. The concept of 'Safety by design', coined around 2005, describes ap-

proaches that prioritize user safety in the design and development of products and services.[16] For a food or feed producer, safety of the product is key. Therefore, from the very start, safety has been integrated into the design of the production process and the production microorganism. *Bacillus subtilis* was chosen as the parent microorganism, to which the European Food Safety Authority (EFSA) has granted 'Qualified Presumption of Safety' status.[17] This means that the microorganism is considered intrinsically safe. *Bacillus subtilis* was then engineered to be sporulation-deficient and to overproduce vitamin B_2. Sporulation-deficient mutants not only support a more stable and efficient production process but also prevent long-term survival in the environment in case of accidental release.[18] As a result of the molecular biology techniques available in the 1990s, the initial vitamin B_2 production strains retained antibiotic resistance markers, which were 'coupled' to the genes to be introduced and helped to select the few bacterial cells which had taken up those genes.[19] However, the antibiotic resistance genes were no longer present in the commercial vitamin B_2 products, since the recombinant DNA had been degraded to undetectable levels in the downstream process. Since then, significant technological progress has been made, and genetic engineering has become much more straightforward and precise, as exemplified by the advent of the genome editing technologies such as CRISPR/Cas9.[20] Accordingly, the current production strains no longer contain antibiotic resistance markers.

The following may inspire reflection: once a target product has been approved for placing on the market, both the production microorganism and the process need to be continuously improved to stay competitive. In the vast majority of cases, this is accompanied by a higher yield, lower raw material consumption and waste production and therefore a lower ecofootprint, and often higher initial purity of the target product. At the same time, the tools for genetic engineering have become much more precise over time. In addition, analysis of the production strain by whole-genome sequencing has become routine. This has resulted in higher process efficiency, associated economic benefits, and an even stronger safety narrative. To leverage the benefits for producers, consumers, and the environment alike, it is imperative that such improvements can be introduced swiftly into the market. In sharp contrast, the current approval process in the European Union demands considerable investment both in terms of time and data requirements. To overcome this obstacle, it would be desirable for the regulatory requirements to become proportionate to the actual safety risks, *e.g.* by using – for already approved products – a notification rather than a formal approval process for further strain improvements.

3. While Non-Synthetic, Bio-Canthaxanthin is Not Necessarily More Sustainable

Canthaxanthin is a natural orange-yellow carotenoid pigment and a potent lipid-soluble antioxidant. It is found in various plants, algae, and bacteria. It is commonly used as a feed (>95%) or food additive (<5%) to provide pigmentation to poultry[21] and both farmed and ornamental fish,[22] as well as to certain food items such as confectionery and beverages,[23] making them more visually appealing to consumers. In addition, canthaxanthin supports reproductive health in poultry[24] and has potent antioxidant properties, which help protect cells from damage caused by free radicals.

The first commercial chemical production process was developed by Otto Isler and Peter Schudel and implemented by Hoffmann-La Roche in 1964.[25] Still today, virtually all commercial production of canthaxanthin is by chemical synthesis.[22] In the early 2000s, Microbia based in Lexington, MA, USA, pioneered the development of biotechnological processes for the production of ketocarotenoids and xanthophylls (*i.e.* astaxanthin, canthaxanthin and zeaxanthin[5]). An oleaginous yeast, *Yarrowia lipolytica,* was selected as production host, to allow accumulation of high amounts of the lipophilic carotenoids. An extensive scientific literature review confirmed the intrinsic safety of this yeast,[26] which was later granted QPS status for production purposes by the European Food Safety Authority.[27]

Microbia was acquired by DSM in 2010. In 2017, due to increasing demand from customers, a dedicated project was launched to explore ways of increasing the manufacturing capacity for canthaxanthin. Expansion of the chemical production plant would have required disproportionate investment and significant downtime. Accordingly, leveraging the biotechnological *Yarrowia lipolytica* platform was seen as a more attractive option. The yeast was genetically engineered to overproduce canthaxanthin, the safety of which has recently been confirmed by EFSA,[28] close to four years after submission of the regulatory dossier in the European Union in March 2021. Approval by the European Commission is expected in the second half of 2025. The fermentation-derived product became available to the first customers in other regions in 2024. For the foreseeable future, the mainstream commercial product will thus remain to be the one obtained by chemical synthesis.

In terms of environmental benefits as determined by a carbon- and eco-footprint analysis, the case is currently less clear and compelling for the fermentation-derived canthaxanthin product than for vitamin B_2. Greenhouse gas emissions that occur throughout the entire life cycle of a product, from the extraction of primary raw materials to processing and waste disposal, determine the carbon footprint. For canthaxanthin, the carbon footprint is highly dependent on the location of the production plant, and whether fossil energy sources (coal or natural gas) are used or not. Furthermore, the origin of the raw materials plays an important role: for the fermentative production of canthaxanthin, lipids are a far more suitable carbon source than carbohydrates due to (a) the nature of the production microorganism, *Yarrowia lipolytica* (note: '*lipolytica*' meaning lipid-degrading) and (b) the highly hydrophobic nature of canthaxanthin, having 40 carbon atoms, but only two (oxygen) heteroatoms. Soy oil has therefore been chosen as the preferred carbon source. Soy sourced from recently deforested areas or areas with a high deforestation risk has an inferior carbon- and eco-footprint than soy sourced from traditional agricultural land with no or low deforestation risk, as shown in Fig. 1.

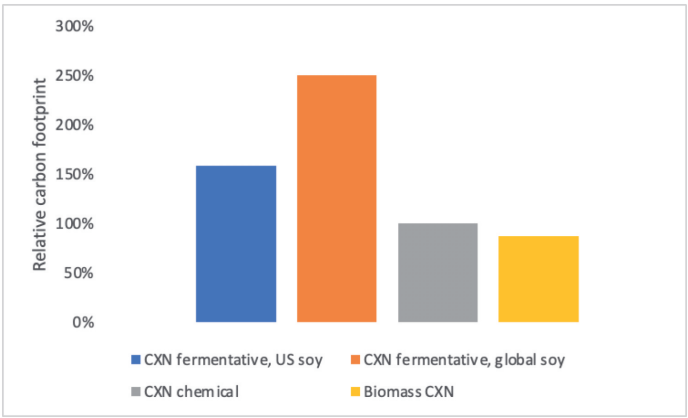

Fig. 1. Carbon footprint of canthaxanthin (CXN) production. Blue column: Fermentation plant in the USA, soy sourced and processed in the USA; orange column: fermentation plant in the USA, soy sourced on the global market, imported into and processed in the USA; grey column: dsm-firmenich chemical process, production site in France (set as 100%), yellow column: fermentation plant in the USA, soy sourced and processed in the USA, potential direct use of biomass (process not yet used commercially). Carbon footprints have been calculated based on Life Cycle Assessment (LCA) according to ISO 14040/44, using the LCA software SimaPro 9.4.0.2 Analyst and the impact assessment method IPCC GWP 100 a 2021; primary data were used from own production sites, secondary data from EcoInvent 3.9.

There would be a straightforward opportunity though to further reduce the carbon footprint of biotechnological canthaxanthin production. Regulatory frameworks have traditionally been developed with chemical products in mind and with the expectation that food and feed products will need to be highly purified to remove non-natural intermediates and side products. Purification ensures the safety, efficacy, and consistency of chemical products. Accordingly, in dsm-firmenich's current biotechnological production process, the canthaxanthin is first purified from the fermentation broth, and is then 'diluted' to the commercial product form by addition of formulation ingredients and an antioxidant. However, in biotechnological production, such stringent purification is not always necessary. For instance, when producing a feed additive by fermentation, the broth inherently contains a mixture of proteins, lipids, and carbohydrates. If an intrinsically safe production microorganism is used (*e.g.* a QPS organism for which no safety concerns are known), purifying the target product and thereby removing the biomass would not only be an unnecessary step but also a waste of valuable nutrients that are already present in a form suitable for animal consumption.

However, there is a challenge: even if the canthaxanthin-enriched biomass contained no live cells of *Yarrowia lipolytica* – and although the legal texts are not entirely clear – such a biomass product, according to current interpretation of the EU biotechnology regulations, would likely need to be considered as a deliberate release into the environment and fall under the genetically modified food and feed regulation (EC) No. 1829/2003. It would thus need two approvals in Europe: one under Reg. (EC) No. 1829/2003, and the other as a feed additive under Reg. (EC) No. 1831/2003. However, regulatory bodies have virtually no experience with such products currently, which risks delaying the approval process unnecessarily. Impossible Foods Inc. has chosen this path for its soy leghemoglobin which is produced by precision fermentation, is used in their Impossible Burgers, and has been shown to contain recombinant DNA. Their dossier was submitted to the European Union in October 2019. In 2024, EFSA adopted two scientific opinions confirming the safety of the product[29] and of the production strain.[30] It is currently unclear when the European Commission will grant regulatory approval. In comparison: Impossible Burgers have been on the US market since 2016, with seemingly no safety issues.

In conclusion, all of the above challenges question the traditional regulatory mindset and highlight the need for a more flexible and proportionate framework that accommodates the unique aspects of biomanufacturing. If confirmed to be free of viable cells, it is proposed that biomass products qualify as contained-use products and only require a single approval, *e.g.* as a feed additive.

4. Bio-Vitamin A – Balancing Sustainability Benefits With Capital Cost of Implementation

Vitamin A is a generic term for a group of fat-soluble diterpene compounds related to retinol. It occurs in two main forms in the diet: preformed vitamin A (from animal products, fortified foods, and supplements) and provitamin A carotenoids (from plant foods), with beta-carotene being most efficiently converted into retinol. Adequate vitamin A supply is crucial for vision, immune function, growth, and reproductive health. In a report published in 2009, the World Health Organization estimated that 190 million preschool children (one-third of children under five) and 19 million pregnant women in developing countries suffer from vitamin A deficiency.[31] Vitamin A deficiency not only leaves populations with weakened immune systems, but also is one of the leading causes of preventable childhood blindness and death. And although the situation has somewhat improved since then,[32] vitamin A deficiency remains a serious health threat, particularly in sub-Saharan Africa.

In the 1930s and 1940s, vitamin A was isolated commercially from oil extracted from the liver of marine animals such as turbot, tuna, halibut, sharks, and whales.[33] It was first commercialized by Hoffmann-La Roche in 1948, and to this day almost all vitamin A produced worldwide is obtained by chemical synthesis using fossil raw materials. Since vitamin A itself is unstable, most commercial products are esterified forms of retinol, with all-trans retinyl acetate being the most prominent. Roughly 70% of the global demand is as a feed additive, with the remaining 30% going to food and pharmaceutical applications.

The chemical manufacturing process for vitamin A used in dsm-firmenich's Swiss production facility is highly optimized and mature. However, the process is very complex and involves fifteen steps requiring a wide range of chemicals, including stoichiometric quantities of base metals such as lithium and magnesium. The preparation of these base metals requires reducing agents, large amounts of energy and produces salt waste that further contributes to the environmental burden of production.

In 2017, a project was started to expand dsm-firmenich's production capacity for all-trans retinyl acetate through development of a new, more sustainable process relying on renewable raw materials. This was accomplished by building on *Yarrowia lipolytica's* known ability to produce beta-carotene,[34] which was then further modified to express a series of enzymes to convert beta-carotene to retinal, retinol and finally retinyl acetate. In conjunction with this, a downstream process was developed to isolate and purify retinyl acetate from the fermentation output, matching the quality specifications of the synthetically produced material. To be successful, several key breakthroughs were required, including: (i) design of optimized variants of the key enzymes beta-carotene oxidase[35] and retinol acetyl transferase;[36] (ii) reconstitution and optimization of the entire pathway in *Yarrowia lipolytica*;[37] (iii) development of a two-phase fermentation process through which retinyl acetate is extracted in an organic phase as the strain produces it;[38] and (iv) development of a high-yield isolation process that crystallizes the retinyl acetate directly from the organic phase. Overall, over 20 patent applications have been filed, many already granted.[39] The process has been validated at pilot scale, and although further strain and process improvements are required, the estimates for the variable production costs are already approaching those of the chemical process.

Fig. 2 shows a comparison of the carbon footprint of the new biotechnological production process in comparison to currently implemented chemical processes. The orange bar shows the relative carbon footprint of retinyl acetate using chemical production processes established in Europe,[40] with European electricity grid and natural gas as energy sources, and comprising all process steps, from cradle to grave. The green bar shows the carbon footprint of manufacturing *via* an industrial route established in Asia and based on the Asian electricity grid (mainly based on coal) and heat supply by coal firing. The blue bar shows the carbon footprint of the fermentative approach as validated at pilot scale and if implemented in Switzerland, starting from ethanol as the carbon source and using Swiss grid electricity and natural gas as the heat source. With further strain and process improvements, the carbon footprint would be reduced even more.

The large difference in carbon footprint between the orange and the green bar in Fig. 2 can be explained by the big difference in GHG emissions from coal firing for heat/steam supply *vs.* natural gas as a heat source, which is more broadly used in Europe. Still, the chemical routes all show a much higher environmental burden compared to the fermentative process. The higher carbon footprint of the chemical process compared to the fermentative route is largely due to the use of energy intensive chemicals: base metals and phosphorous-based coupling of building blocks. On the other hand, the superior sustainability profile of the biotechnological process is due to the intended use of a renewable primary

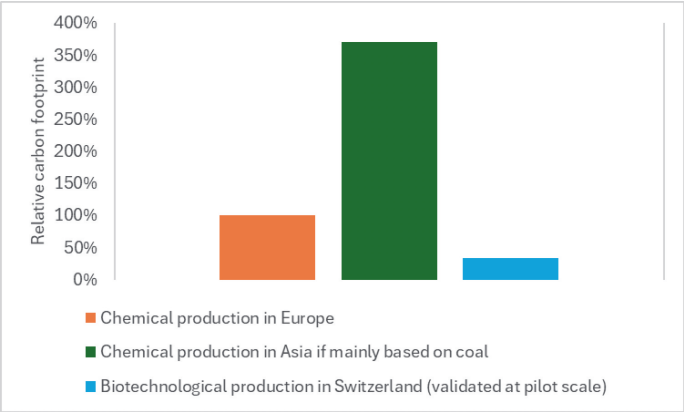

Fig. 2. Relative carbon footprint of different production processes for vitamin A (retinyl acetate).[1] Orange column: current chemical processes established in Europe relying on natural gas as the energy source (set as 100%); green column: chemical producers using coal as the energy source for steam and electricity; blue column: dsm-firmenich's new biomanufacturing process, at current technological maturity level as established at pilot scale. Carbon footprints have been calculated based on Life Cycle Assessment (LCA) according to ISO 14040/44, using the LCA software SimaPro 9.4.0.2 Analyst and the impact assessment method IPCC GWP 100 a 2021; primary data were used from own production sites, secondary data from EcoInvent 3.9. Plausible assumptions were made about the process efficiencies achieved in different processes implemented across the globe.

carbon source with a low carbon footprint (ethanol), significant process simplification, and much lower energy requirements.

Implementing a more sustainable process that meets the market's quality expectations is only possible if it can be done in a cost competitive manner. This consideration becomes most important with implementation of this process in Europe. Due to significant differences in raw material and energy prices, the variable production costs of this process alone would be approximately 25% higher in Europe than in the United States. This would have severe implications on the competitiveness in the global markets. The other obstacle to implementation, which is independent of geography, is the capital investment needed to establish the biomanufacturing facility in light of the largely depreciated existing production facilities using the chemical processes. This could be partially offset *via* investment subsidies and/or favourable tax arrangements. Thus, decisions to implement the bio-vitamin A process, including location, will critically depend on favourable economic and regulatory framework conditions, the measures taken to support the switch to a (bio-) economy based on renewable raw materials, and the incentives created by governments to attract innovation and investment, as further outlined below.

5. Policy Action is Required to Support Industry in Addressing the Global Challenges

5.1. *The Challenges We Need to Face*

The Earth is facing a number of intricately interlinked, man-made global crises. The risks of global warming, which is primarily due to the burning of fossil resources, include a higher frequency of extreme weather events, rising sea levels, water scarcity in other regions, and associated social implications such as health threats, economic losses, as well as social and political instability. Global warming also has a significant impact on biodiversity which is experiencing an unprecedented decline; it has been estimated that the current extinction rate of vertebrate species is approximately 35-times higher than in preindustrial times.[41] To preserve a healthy planet for generations to come, including the ecosystem services needed for a flourishing economy as a basis for health and wealth, proposals have been made on the planetary boundaries that need to be respected.[42] In addition, the Paris Agreement under the United Nations Framework Convention on Climate Change has set ambitious goals to limit global warming to below 2.0 °C and preferably below 1.5 °C.[9] This, in turn, will require a reduction in anthropogenic CO_2 emissions to 'net zero' by the middle of this century.[43]

To achieve 'net zero', fundamental changes are required in the ways we live, produce, and consume. Energy supply needs to be fully decarbonized, *i.e.* we need to move away from coal, oil and natural gas. The raw material base for manufactured goods needs to be 'de-fossilized' through a switch to renewable raw materials. Energy consumption and waste generation need to be minimized wherever possible, and the efficiency of production processes thereby maximized. In short: we need to transition from the current economic model which is heavily reliant on a 'take-make-waste' approach towards a circular, no-waste (bio-) economy based on renewable raw materials. All these constraints will offer ample opportunities for innovation in the (bio)chemical manufacturing industry which is currently estimated to contribute 5–9% to the global greenhouse gas emissions.[44]

The importance of the above transformations has been realized by the European Commission and is reflected in its ambition to boost biotechnology and biomanufacturing.[12] The forthcoming EU Biotech Act, anticipated to be published in 2026, aims to establish ambitious and effective incentives and framework conditions for biotechnology and biomanufacturing. This initiative will hopefully aspire to position the European industry as a leader, while simultaneously boosting its competitiveness and ensuring significant contributions to the sustainability goals of the EU Green Deal and the United Nations' Climate and Biodiversity Conventions.

5.2. *Key Learnings from Real-life Examples*

The three biomanufacturing examples highlighted in this article, vitamins A and B_2 as well as canthaxanthin, are evidence of our company's commitment to more sustainable production processes for important ingredients used in human and animal nutrition. Three key learnings can be derived from these examples: (1) Biomanufacturing can offer significant economic and environmental benefits compared to chemical production, as shown compellingly for vitamins A and B_2. However, as evidenced by the canthaxanthin example, this is not invariably the case; thus, a case-by-case assessment is required to compare all available process options. (2) Sustainability benefits are context-dependent, with the use of renewable *vs.* fossil-based energy having a strong impact on the eco-footprint (see Fig. 2). The same is true for use of sustainably sourced soy *vs.* soy that is associated with a high deforestation risk (see Fig. 1). (3) Additional sustainability benefits could be realised if we were able (and regulations encourage) to move away from today's default approach of highly purified chemical products and establish, for instance, biomass products on the animal nutrition and health market (see Fig. 1).

5.3. *What Does this Mean in Terms of Opportunities for Europe?*

To move towards a future-proof economy respecting the planetary boundaries, Europe can build on the strengths of its educational systems and of its chemical industry. It can leverage its strong academic community to develop the best combinations of strategies and technologies, including biotechnology, biomanufacturing and green chemistry, to enable a far-sighted circular (bio-) economy. This, in turn, will create interesting job opportunities, also in rural areas, due to an increasing reliance on renewable, bio-based raw materials. In addition, experience from the past few decades has shown us that due to different economic and regulatory framework conditions, global production of critical goods

may be concentrated in one or just a few areas on the globe. One example is critical medicines and their ingredients, in particular generic drugs, for which Europe is heavily dependent on China and India. The same is true for vitamins, where most of the global production capacity is in the Far East. Investments in a circular (bio-) economy can thus be seen as an instrument to increase the independence and resilience of Europe.

An important prerequisite for implementation in Europe is competitive costs for carbon feedstocks and energy which make up more than 70% of the variable production costs of fermentation products such as the three examples featured in this article. However, looking back at the past 10 years, market prices for glucose and ethanol were 40–70% higher in Europe than, for example, in the USA. In addition, price fluctuations over time were considerably larger for bio-based raw materials than for base chemicals such as toluene, which directly impacts the competitiveness of bio-based *vs*. chemical products on the global markets. For the required transformation to succeed, energy and raw material costs in Europe need to be competitive *vis-à-vis* other regions, and they need to be sufficiently stable and/or predictable. Lifting of import taxes on carbon feedstocks for specific use in the biomanufacturing of specialty chemicals would be a critically needed first step to improve the cost competitiveness of the European biomanufacturing industry.

A thorough review and update is also required of the regulatory framework conditions for biotechnology which were originally established in 1990, based on the scientific knowledge available at that time. A lot of technological progress has been made since then, as exemplified by the development of genome editing techniques such as CRISPR/Cas9.[20] Further 'safety-by-design' is an established best practice for all those developing microbial production strains for precision fermentation processes. In addition, it is now possible to determine the complete genome sequence of a microbial production strain, allowing the confirmation and/or identification of all intended and non-intended genetic modifications. Finally, there is much more knowledge on and experience with genetically engineered organisms, resulting in a better comprehension of both risks and opportunities. As a result, (i) much more is now known about the value and risks associated with genetic engineering, and (ii) the current regulatory framework is no longer fit-for-purpose. In the interest of supporting the transition to a circular bio-based economy, the following enhancements can be considered: (a) a move away from the current process-centric approval system for biotechnology products where the main emphasis is on the process of how a strain has been developed or improved (GMO *vs.* non-GMO) towards a product-centric approval system in which the regulatory burden shall be proportionate to the actual safety risks. In particular, for no or low safety risks, a notification process could and probably should be offered. (b) Along the same lines: for products and production processes that have been previously authorized, swift implementation of further process improvements will be key to encouraging investment in order to stay competitive here in Europe. (c) To avoid regulatory uncertainty and to create space for further sustainability improvements, the presence *vs*. absence of live cells of the production microorganism should be the only criterion for fermentation products that distinguishes between deliberate release into the environment *vs.* contained use, and whether the product would fall under the genetically modified food and feed Reg. (EC) No. 1829/2003. In contrast, absence of recombinant DNA should not be used for regulatory classification[45] and should only be required for production microorganisms containing sequences of safety concern, as part of the safety assessment by the European Food Safety Authority (EFSA).

Due to a higher technical readiness level, many industrial fermentation processes currently depend on first-generation carbon feedstocks (*e.g.* carbohydrates from sugar cane, sugar beet or corn) and thereby compete with food production for land or materials. Attempts to use second- or third-generation bio-based feedstocks or even CO_2 from the atmosphere are underway but still require further development before being a viable alternative. We urge caution in placing restrictions on the use of first-generation feedstocks for the biomanufacturing of specialty chemicals at this time. Such restriction would negatively impact innovation, deter investment, and therefore delay the transition to a circular bio-based economy. Parallel development of (i) cutting-edge fermentation processes for specialty chemicals using first-generation feedstocks and (ii) robust microbial production platforms for using second- or third-generation feedstocks and then combining these technological advances seems the most appropriate approach to speed up the de-fossilization of the chemical industry.

Finally, as highlighted by, *e.g.* Gabrielli *et al*.[43] the chemical industry strongly relies on capital-intensive and long-lived assets and requires significant investments to change its asset base. To achieve 'net zero' by 2050, the right framework conditions need to be created with urgency. According to Philp, governments should invest in bio-based manufacturing to more quickly penetrate the marketplace.[46] In any case, an attractive business case for biomanufacturing in Europe requires financial incentives and/or demand security. Otherwise, investments will continue to be considered too risky. Another success factor will be the availability of cost-competitive and versatile facilities for piloting and demo-scale production to reduce the risk of large investments in new commercial biomanufacturing facilities.

In conclusion, progressing towards net-zero anthropogenic greenhouse gas emissions by the middle of the 21st century requires bold moves by both private investors and governments. We hope that the examples and insights presented in this paper will inspire thoughtful approaches to overcoming the challenges ahead.

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