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Can biotechnology lead the way toward a sustainable pharmaceutical industry?☆

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The impact-intensive and rapidly growing pharmaceutical industry must ensure its sustainability. This study reveals that environmental sustainability assessments have been conducted for only around 0.2% of pharmaceuticals, environmental impacts have significant variations among the assessed products, and different impact categories have not been consistently studied. Highly varied impacts require assessing more products to understand the industry's sustainability status. Reporting all impact categories will be crucial, especially when comparing production technologies. Biological production of (semi)synthetic pharmaceuticals could reduce their environmental costs, though the high impacts of biologically produced monoclonal antibodies should also be optimized. Considering the sustainability potential of biopharmaceuticals from economic, environmental, and social perspectives, collaboratively guiding their immense market growth would lead to the industry's sustainability transition.

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The proliferating and polluting pharmaceutical industry

The essentiality of sustainable development as defined by the United Nations [1] has become increasingly clear, and a sustainable industry is a key part of ensuring it [2,3]. Sustainability must include three integrated pillars: economic, social, and environmental sustainability [4]. Environmental sustainability can be quantified based on 12 impact categories: climate change (CC), abiotic resource use, photochemical ozone formation, ozone depletion, ecotoxicity, human toxicity, acidification, eutrophication, land use, water consumption, particulate matter formation, and ionizing radiation [5]. Among these, CC has been given particular attention to limiting global warming below the internationally agreed limit of 1.5°C [3,6]. In parallel, the importance of comprehensively ensuring the sustainability of all the environmental categories has become clear [7•,8].

The pharmaceutical industry (per unit of product mass) is among the most resource-, energy-, and pollution-intensive industry sectors [9,10••,11], and the consumption of pharmaceuticals has been increasing steadily [12]. In the last decade, global per capita pharmaceutical consumption in defined daily dose (DDD), as standardized by the World Health Organization [13], has shown a steady rise with a compound annual growth rate (CAGR) of 2.4% [12] (Figure 1a). This trend is expected to continue in parallel with the aging population and widening global access to health care [12,14]. Major bulk chemical industries have not followed the same trend, as illustrated by per capita production plastics [15–17], fertilizers [18], paper materials [19], and cement [20,21] (Figure 1a). The infeasibility of storage, recycling, or reuse of pharmaceuticals, also contrasting most bulk chemicals, necessitates ensuring the responsible production of pharmaceuticals toward a sustainable future. Regarding the environmental impact intensity, Figure 1b illustrates that the CC impacts of pharmaceuticals are degrees of magnitude apart from bulk chemicals, as compared by different anesthetic active pharmaceutical ingredients (APIs) and bulk plastic types [10••,22].

Reducing dependencies on fossil-based resources and often characterized by lower CC impacts, biological production routes are considered central to a sustainable industry ecosystem [7•]. Accordingly, there has been growing investment in exploring bio-based production routes to replace traditional alternatives [7•,23••], and

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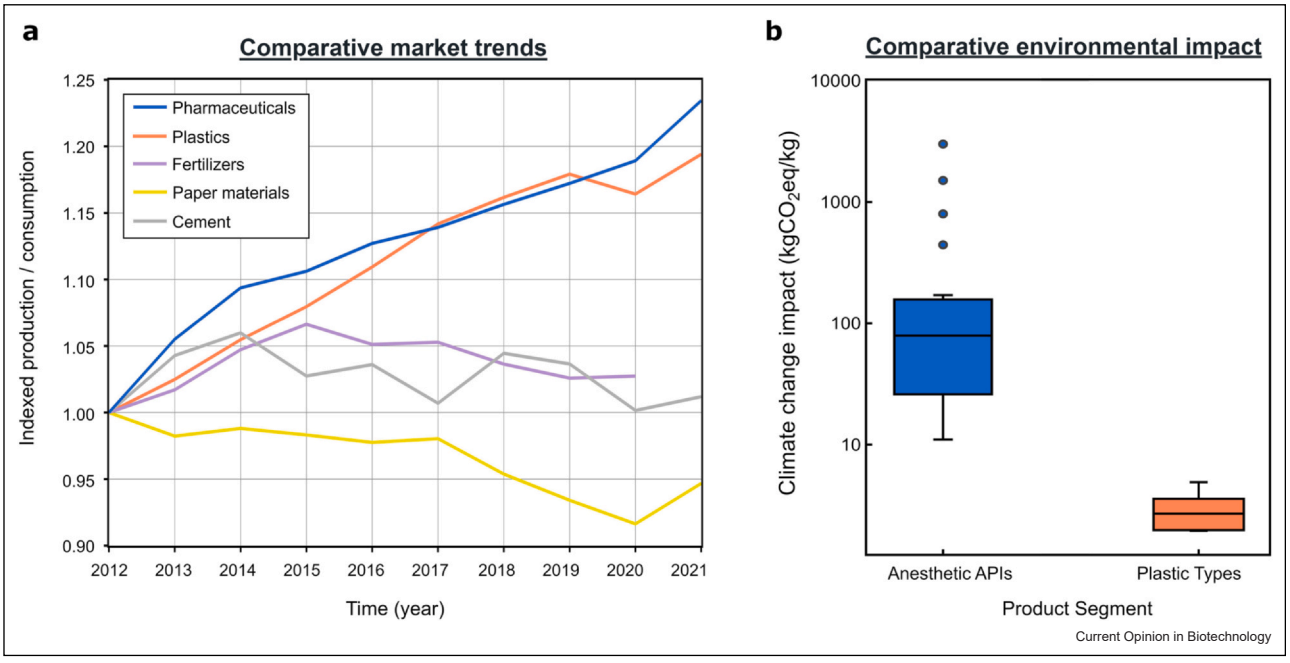
Figure 1



Market and environmental impact trends among different product srgments **(a)** Indexed market trends for global pharmaceuticals consumption in DDDs [12] and plastics [15–17], fertilizers [18], paper materials [19], and cement [20] production in mass per capita (global population data were referred to the United Nations [21]). **(b)** Comparative CC impact of different anesthetic APIs [10••] and different plastic polymers [22].

novel bio-based processes are being developed in various industry segments, such as polymers [24], construction materials [25], platform chemicals [26], as well as pharmaceuticals [27]. From a scientific perspective, methodologically quantifying the impacts of any production route is crucial to guide and ensure their sustainability performance [7•,8].

This review presents current reporting on the pharmaceutical industry's sustainability. Biotechnology's potential for cleaner production is described by analyzing the data by production routes. In addition, the biopharmaceutical industry's status is presented with the merits and challenges of biotechnology for sustainable production. Guidelines of interdisciplinary collaboration are described toward optimally guiding the pharmaceutical industry toward sustainability.

What do we (not) know about the sustainability state of the pharmaceutical industry?

Assessing the environmental sustainability performance of commercial products is necessary to guide product innovation and industries' transition toward sustainable development. Life cycle assessment (LCA) is a scientific tool identifying hotspots and trade-offs within a system life cycle [28]. Comprehensive LCA studies cover all life cycle stages and relevant environmental impact categories; among them, CC has been prioritized globally. However, categories such as eutrophication, human toxicity, and/or water consumption are highly relevant for the pharmaceutical sector to ensure that it does not overlook unexpected environmental burdens [29]. Recently, performing LCA of biochemical production at early stages has been addressed as an approach to shifting biochemical production to a more sustainable industry [7•]. It involves identifying key environmental hotspots, estimating commercial-scale process data for early-stage LCA, and using environmental performance outcomes to promote more sustainable alternatives. Parallelism could be brought to pharmaceuticals, so the authors see an opportunity to implement early-stage sustainability assessments to guide the pharmaceutical industry's sustainability transition. From a global perspective, the sustainability challenge should be translated into planetary impact quantification to ensure the estimation of humankind's safe operating space (SOS) before it irreversibly damages the biosphere. These limits were provided by the planetary boundaries framework [30], where the guidance of pharmaceuticals should also consider its own SOS.

We analyzed the environmental assessments concerning pharmaceuticals in the literature (Table 1) to illustrate the present performance of this industry by reporting assessed pharmaceutical compounds and LCA impact categories as classified by Hauschild et al. [5]. Accordingly, 24 publications evaluated 36 specified pharmaceuticals, two APIs with

Table 1

Published environmental impact assessment studies of pharmaceuticals by the compound and studied impact categories. In the compound backgrounds, red, blue, and green, respectively, represent synthesis, extraction/semisynthesis, and fermentation production routes [10••,11,32-34,38,40,41,42•,54-59,60•,61-67, 68•].

Study	Compound	Impact Categories [5]												Categories Studied (%)
		Climate Change	Photochemical Ozone Formation	Ozone Depletion	Abiotic Resource Use	Ecotoxicity	Human Toxicity	Acidification	Eutrophication	Land Use	Water Use	Particulate Matter Formation	Ionizing Radiation	
Wang et al. [32]	Ibuprofen	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	100%
Sharma et al. (I) [54]	Paracetamol	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	92%
Sharma et al. (II) [40]	Paracetamol	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	92%
Pietrzykowski et al.[55]	mAb (unspecified)	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	92%
Cespi et al.[56]	Sildenafil	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	92%
Amasawa et al.[42](•)	Nivolumab	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			83%
Güne & engül [38]	Chlorhexidine gluconate Benzydamine hydrochloride	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		83%
Ott et al. (I)[57]	Rufinamide	✓	✓	✓	✓	✓	✓	✓	✓	✓				75%
Ott et al. (II)[58]	Confidential API	✓	✓	✓	✓	✓	✓	✓	✓	✓				75%
Kong et al.[59]	Enrofloxacin	✓	✓	✓	✓	✓	✓	✓				✓		67%
Riazi et al.[60](•)	Isostearic Acid	✓		✓	✓		✓	✓	✓	✓	✓			67%
Alviz & Alvarez[61]	Aspirin	✓	✓	✓	✓	✓	✓	✓	✓					67%
Yang et al.[62]	Ciprofloxacin hydrochloride	✓	✓	✓	✓	✓	✓	✓				✓		67%
Harding et al.[63]	Penicillin	✓	✓	✓	✓	✓	✓	✓	✓					67%
Jimenez-Gonzalez[64]	Sertraline	✓	✓	✓		✓	✓	✓			✓			58%
Lee et al.[65]	4-d-Erythronolactone	✓	✓		✓	✓		✓	✓		✓			58%
McAlister et al.[66]	Morphine	✓	✓	✓		✓	✓				✓			50%
Kim et al.[67]	3 pharmaceutical enzymes (confidential)	✓	✓					✓	✓					33%
De Soete et al.[34]	Tramadol	✓			✓					✓	✓			33%
Renteria Gamiz et al.[68](•	Infliximab	✓						✓	✓					25%
Bunnak et al.[41]	mAb (unspecified)	✓									✓			17%
Parvatker et al.[10](••)	Lidocaine Bupivacaine HCl Ropivacaine HCl Phenylephrine HCl Fentanyl Ephedrine HCl Succinylcholine Ondansetron Midazolam Glycopyrrolate Rocuronium bromide Epinephrine Remifentanil Sugammedex Ketamine Dexmedetomedine Hydromorphone Morphine Propofol	✓												8%
Brunet et al.[33]	Penicillin	✓												8%
Wernet et al.[11]	Confidential API	✓												8%
Fraction of pharmaceuticals [31] **with environmental assessment:** 0.2%		100%	71%	67%	67%	67%	67%	67%	63%	46%	42%	33%	21%	?
		Category Inclusion (%)												

confidential identities, three unspecified pharmaceutical enzymes, and two unspecified monoclonal antibody (mAb) production processes. Therefore, considering more than 20 000 Food and Drug Administartion–approved drugs [31], environmental sustainability assessments have only been conducted for approximately 0.2% of the existing compounds (Table 1).

Regarding different LCA impact categories (Table 1), only the CC category was reported in all (100%) of the found publications. Photochemical ozone formation (71%), ozone depletion (67%), abiotic resource use (67%), ecotoxicity (67%), human toxicity (67%), acidification (67%), and eutrophication (58%) were reported in nearly two-thirds of the studies. Land use (46%) and water consumption (42%) were, respectively, assessed in circa half and two-fifths of the studies. Particulate matter formation was considered in one-third (33%) of the studies, and ionizing radiation was the least considered category (21%). Since the performance of different impact categories is not correlated, that is, a product's relatively low impact in one category does not indicate likewise small impacts in other categories, consideration of different impact categories is crucial to understanding the industry's sustainability status.

Only one study [32] covered the results of all the environmental impact categories, while three studies exclusively reported CC impacts [10••,11,33]. The remaining 19 studies reported the outcomes of multiple but not all the impact categories. In addition, 23 of the 24 studies considered the life cycle stages by the production line (i.e. cradle-to-gate), while one study [34] further included the distribution to the pharmacies stage (cradle-to-pharmacy gate). Expanding the scope of the studies to cover the full life cycle (i.e. cradle-to-grave) is essential to optimize the industry holistically, as the potential impacts of storage [9,35], use [36], and end-of-life [9,36,37] stages have been emphasized for the pharmaceutical industry. Moreover, as illustrated in Figure 1b, the magnitude and standard deviation of the reported CC impacts of pharmaceuticals, even in the same drug category as anesthetics, vary drastically. Thus, it is necessary to assess the compounds individually rather than predicting current and future impacts based on existing studies.

Pharmaceuticals feature especially high impacts in ecotoxicity [32,38,39], human toxicity [32,38–40], and water consumption [40–42•] categories. Hence, considering these categories will be especially important to guide the pharmaceutical industry toward sustainability. The European Commission has recently emphasized the inclusion of the ecotoxicity and human toxicity categories in environmental assessments [43]. In relation to the planetary boundaries framework (vide supra), humanity has transgressed the novel entities boundary, which covers ecotoxicity and human toxicity categories [44]. Furthermore, fluorinated compounds of different bonding types comprise roughly 20% of all pharmaceuticals [45] due to their certain properties (e.g. increased bioavailability, tailored molecular steric effects [46]), with production routes potentially inducing per/polyfluoroalkyl substance (PFAS) streams. Though the classification of halogenated bonds regarding their consideration as PFAS is under scientific debate [47], environmental assessment studies of them demonstrated particularly high ecotoxicity and human toxicity impacts [48,49]. In addition to the release of pharmaceuticals into water systems during their production phase, unmetabolized pharmaceuticals from domestic and hospital use also pollute water systems, harmfully affecting the ecosystem quality as well as public health [9,50]. Therefore, concerns have been emerging about the contamination of water systems by pharmaceuticals [50,51], with antibiotics, anti-inflammatory drugs, psychiatric drugs, and β-blockers usually reported among the most detected products causing harmful consequences, including evolution of antibiotic-resistant bacteria and endocrine system dysfunctions in living organisms [37,50,51]. Traditional wastewater treatment processes usually are not designed to remove these compounds [50,51], and environmental assessments indicated that pharmaceuticals and personal care products are the major contributors to the toxicity of water systems [37]. Improved water treatment technologies to clear pharmaceuticals (e.g. catalytic oxidation, adsorption, membrane separation) are currently under development [50]. Likewise, problems related to freshwater shortages have been increasingly reported globally [52,53], and freshwater consumption planetary boundary has already been detected to be beyond the Earth's carrying capacity in several regions (including the Mediterranean, India, North China, California) as well [30].

Briefly, it is revealed that not only a minor fraction of pharmaceuticals has been environmentally assessed but also that the categories, except CC, have not been consistently included in the studies. To have a clear understanding of the sustainability status of the pharmaceutical industry, more pharmaceuticals should be assessed, and the assessments should be comprehensive, involving all the environmental impact categories.

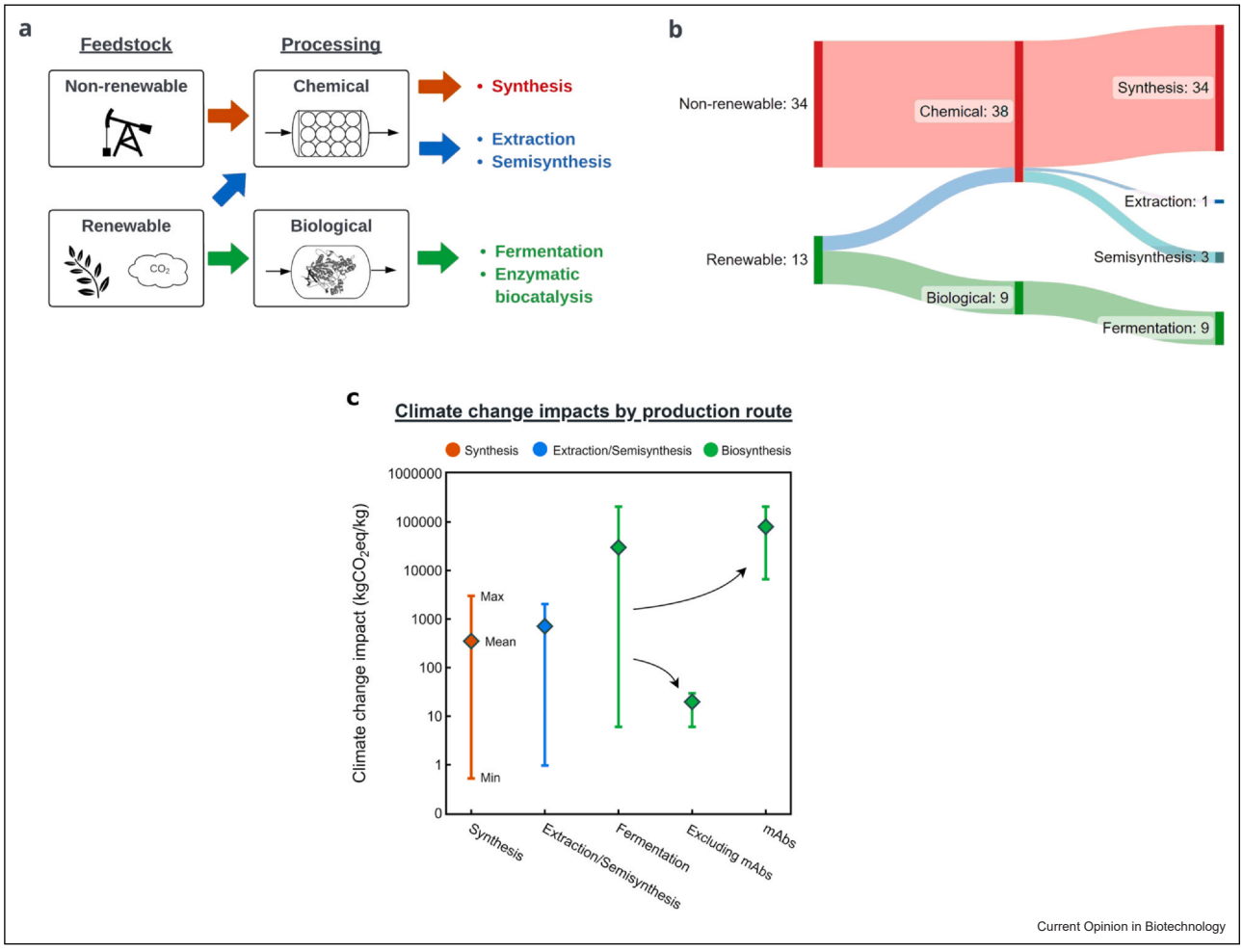
The potential of biotechnology for a sustainable pharmaceutical industry

Biopharmaceuticals refer to the pharmaceuticals of biological origin, produced using engineered host organisms, including plants, animals, bacteria, and fungi [69–71]. Regarding their development, penicillin production using *Penicillium chrysogenum* is considered the first biologically produced pharmaceutical on an industrial scale during the mid-20th century [23••,72]. The introduction of genetic engineering techniques in the 1970s grew the biopharmaceutical market, a noteworthy example being industrial insulin production by recombinant *Escherichia coli* in 1982, the first licensed drug manufactured via recombinant DNA technology [23••,73].

Entering the 2000s, biopharmaceuticals production was accelerated by the genomics revolution enabling modeling of the metabolic networks [23••,74–76] and further developed by advancing synthetic biology [23••,74–76] and metabolic engineering [23••,75,76] techniques. More recently and based on all these advancements, the longest metabolic pathway ever refactored from a plant to a microbial factory (*Saccharomyces cerevisiae*) showcased proof-of-concept microbial production of the two precursors, vindoline and catharanthine, for the semisynthesis of the anticancer drug vinblastine [77••,78]. The advancing biotechnologies, together with the increasing focus on environmentally benign production, particularly related to renewable feedstocks that bioprocesses are known for, have expanded the biopharmaceutical sector significantly [23••,79•,80].

Pharmaceutical production processes can be classified based on the selected feedstock and the processing route (Figure 2a). Nonrenewable feedstocks originate from fossil-based resources, whereas renewable feedstocks include biomass-based sources and carbon dioxide, ensuring the recirculation of end-of-life carbon in the future feedstock [8,23••,27,79•,81,82]. Synthetic pharmaceuticals are produced from nonrenewable feedstocks via chemical catalysis [10••,74,79•]. Extraction refers to extractive purification of target molecules from natural resources, mainly plants

Figure 2



Classification and environmental impact comparison of pharmaceutical production routes **(a)** Pharmaceutical production routes by feedstock type and processing. **(b)** A Sankey diagram depicting the classification of pharmaceutical production routes found in the reviewed LCA studies. **(c)** CC impact ($kgCO_2eq/kg$) data organized based on mean and range of values provided in the found LCA studies. Completely different processes based on different feedstocks [60•] or eventual different products [67] were considered as different data points. In other cases when batch and continuous processing is compared [41,42•,65], minor processing alterations involved such as different solvents [61] or different dosage forms [54] in production of the same API or different scenarios based on information availability [63], average of the provided results is used as a single data point. The first three data sets are based on the processing routes, synthesis (n = 24), extraction/semisynthesis (n = 4), and fermentation (n = 8). The final two data sets show the outcomes of the fermentation processes when mAb production routes excluded (n = 5) and solely the mAb production routes (n = 3), respectively.

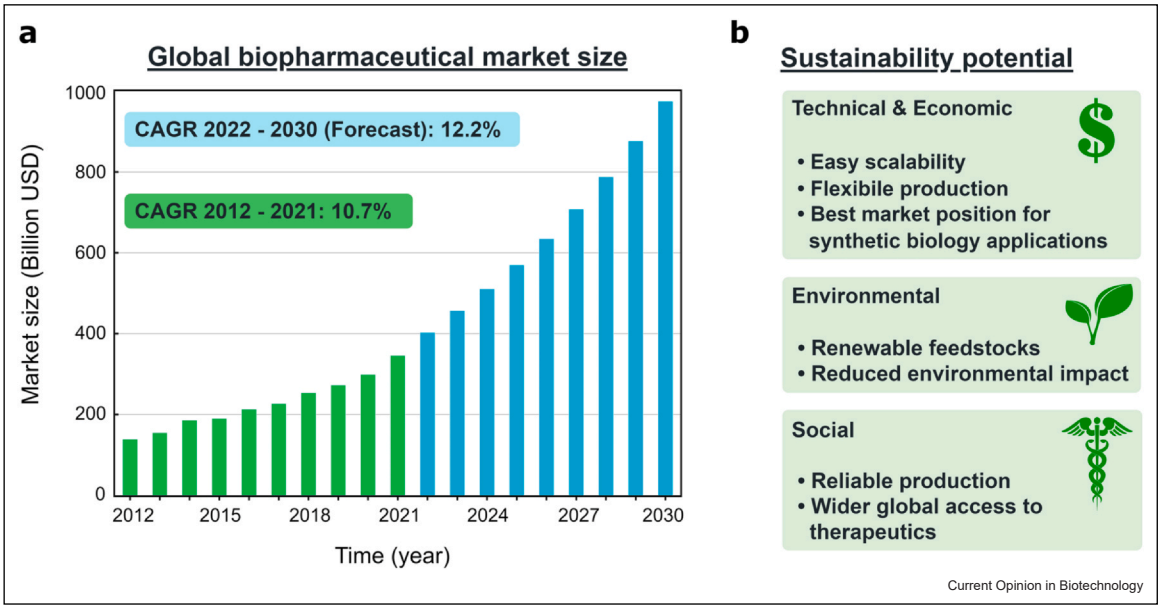
[66,77••]. In semisynthesis, a natural product, usually a plant extract or a microbially produced precursor thereof, is chemically converted into the target molecule [60•,76,77••]. Chemical routes also usually involve harsh separation and purification steps, resulting in toxic outlet streams [10••,66,80]. Finally, biopharmaceuticals are biologically produced by enzymes in microbial chassis from renewable feedstocks [8,79•,80]. Fermentation processes refer to growing the host organism (a.k.a. cell factory) producing the target compound, while enzymatic biocatalysis refers to the usage of purified enzymes *in vitro* for biocatalysis, offering more flexible process conditions by eliminating cell constraints [67,79•].

The processing routes of the analyzed sustainability studies highlight that 34 of the assessed production routes were based on chemical synthesis from materials of nonrenewable origin (Table 1; Figure 2b). Four routes were based on the extraction of renewable feedstocks, three among which were chemically further converted into the target compound via semisynthesis. Nine routes were based on fermentation-based biomanufacturing using cell factories, whereas none of the studies involved enzymatic biocatalysis processes utilizing enzymes *in vitro* without the host organism. Provided data by impact categories were organized to gain insight into environmental performance by process type. The outcomes regarding the CC category are discussed, whereas the data were considered insufficient to draw meaningful conclusions for the remaining impact categories. According to the outcomes (Figure 2c), fermentation-based processing was observed to have the highest mean CC impact value of 29 900 $kgCO_2eq/kg$, followed by extraction/semisynthesis routes by 710 $kgCO_2eq/kg$ and chemical synthesis by 351 $kgCO_2eq/kg$. However, it is noted that mAbs (nivolumab, infliximab, other unspecified mAb products) have significantly higher CC impacts compared with the remaining fermentation-based products (pharmaceutical enzymes, penicillin). Therefore, fermentation-based routes are further subgrouped as mAb products and the remaining biologics (Figure 2c). When mAbs excluded, fermentation routes resulted in a lower CC impact than most synthetic/semisynthetic products, with a mean of 20 $kgCO_2eq/kg$. The large CC impact of mAb products is also emphasized, with a mean of 79 700 $kgCO_2eq/kg$ and a range of 6607–207 000 $kgCO_2eq/kg$. Hence, two preliminary conclusions can be obtained from this analysis. First, biologically synthesizing pharmaceuticals originating from synthesis and extraction/semisynthesis routes can be promising for their cleaner production. Second, regarding the very high environmental impacts of mAbs, also given that mAbs are among the most purchased pharmaceuticals [70,83], particular attention should be given to developing strategies to optimize their production. For instance, substituting animal-sourced materials in their production media can significantly reduce the environmental impacts of mAb production [68•]. Similar analyses can be made for the remaining impact categories after the collection of the relevant data. For instance, as pharmaceuticals tend to have higher environmental impacts in ecotoxicity and human toxicity categories (vide supra), comparing synthetic halogenated API production routes with novel biological routes (e.g. engineering cell factories capable of utilizing halogenated building blocks or incorporating halogenase enzymes into them to produce target APIs from natural nutrients [46]) could affect their environmental performance with potentially different PFAS flows (e.g. due to different reaction efficiency, process control, etc.).

Biopharmaceuticals also offer immense market opportunities from an economic perspective. The global biopharmaceutical market has grown from $139 billion in 2012 to $346 billion in 2021 with a CAGR of 10.7% [84] and been forecasted to reach $975 billion by 2030 with a corresponding CAGR of 12.2% [85] (Figure 3a). In parallel, the share of biopharmaceuticals in the overall pharmaceuticals market has increased from 24% in 2014 to 33% in 2020, which is expected to reach 41% in 2028 [84]. Thus, biopharmaceuticals offer enormous potential for the pharmaceutical industry's sustainability transition if their growth is systematically directed with a sustainability vision. Moreover, 57.2% of the biotechnology sector comprises biopharmaceuticals [86], demonstrating their advantage within the sector considering the accumulated knowledge and infrastructure. Regarding commercialization, as recently reported [87], biologically refactored specialty chemicals are better positioned to reduce production costs compared to commodity chemicals. Furthermore, biotechnology is most feasible for naturally occurring compounds, as the target genes encoding biosynthetic enzymes are already found in nature [87]. Since around two-thirds of the pharmaceuticals are naturally existing products and their derivatives [88], biotechnology offers enormous potential to investigate and develop manufacturing routes for pharmaceuticals with lowered environmental impact. Guidance from a commercial perspective would be involving large pharmaceutical companies in the initial stages of the novel biopharmaceutical technology startups, as such involvements are found to be significantly correlated with commercial success [89•].

Concerning social sustainability, biological processing offers wider accessibility of pharmaceuticals by a decentralized and flexible biomanufacturing supply chain, especially via independent and trustable microbial refactoring routes replacing location-dependent plant extraction processes that are unstable and, correspondingly, expensive [9,46,77••,78,90]. From this perspective, also accelerated by the shortages during the coronavirus disease 2019 pandemic, the pharmaceutical industry has been incentivized to prioritize supply

Figure 3



Biopharmaceutical market trends and features**(a)** Global biopharmaceutical market size over time [84,85]. **(b)** Mentioned sustainability potentials of biopharmaceuticals.

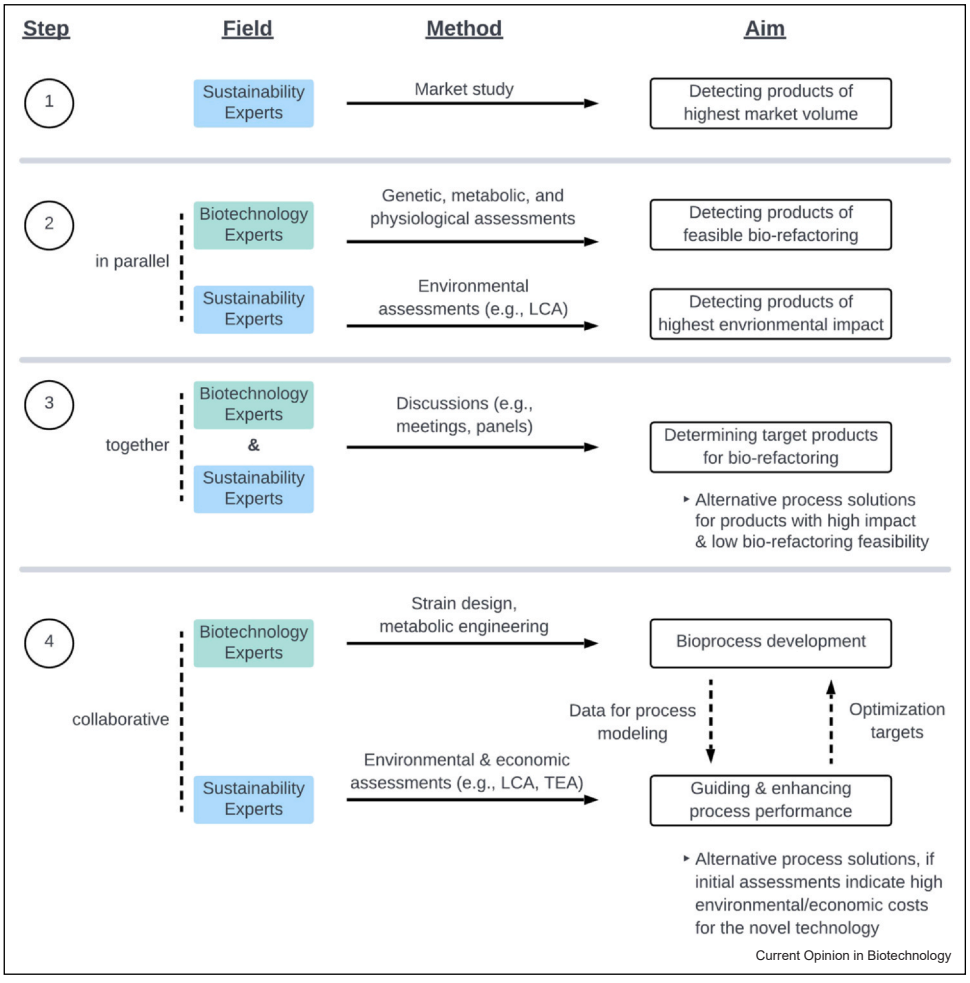
security and reliability [78,91,92]. For instance, EuroAPI, a Sanofi-initiated firm focusing on substituting Europe's reliance on external supply by fermentation-based manufacturing, is expected to dominate the European small molecule API market [91,92]. Quantitative sustainability studies in biotechnology have been usually limited to economic and environmental aspects. The social life cycle assessment (S-LCA) is a tool analogous to LCA that assesses the potential impacts of products concerning various societal aspects, including local employment rate, worker well-being, workplace safety, and gender wage equality [93]. Recent advances in integrating social indicators into the product life cycle have enabled the social sustainability assessment of bioproducts [94], though, similar to the environmental assessments, tracking the social impacts beyond the consumption phase remains a challenge. Thus, consistently integrating social aspects to quantitative sustainability assessments would elucidate the societal benefits of individual production routes. The mentioned advantages of biopharmaceuticals regarding the three pillars of sustainability are summarized in Figure 3b.

An interdisciplinary collaboration for the pharmaceutical industry's sustainability transition

As described, biopharmaceuticals are promising considering various environmental, technical, economic, and social aspects. Moreover, the sector is growing exponentially, and several reasons add to the optimism for commercial success. However, a matter of consideration in refactoring biosynthesis of pharmaceuticals in cell factories, from here to be referred to as "bio-refactoring", is the extensive research and development (R&D) resources required to develop cell factories capable of producing the compound in commercially feasible scales with competitive prices. This development usually takes more than $50 million of financial and 200 person-years of labor resources, with the obtainment of the final strain after a 5- to 10-year journey, depending on factors, such as the complexity of the integrated metabolic pathway and compatibilities with the cellular physiology [77••,78,95,96]. Therefore, with biological production potentially leading the sustainability transition of the pharmaceutical industry, collaboration between sustainability and biotechnology experts is essential to utilize our limited R&D resources efficiently. Targeting compounds of high impact and bio-refactoring feasibility will be crucial, as well as guiding the novel technologies from their early stage to ensure their sustainable development while advancing in the technological readiness levels.

The collaboration strategy between sustainability and biotechnology fields can be conceptualized based on the renowned IPAT (Impact = Population × Affluence × Technology) equation (Equation 1) [97], with terms in the environmental impact context provided in Equation 2. Referring to market volume for the overall product amount, Equation 3 is given. Thus, conceptual Equation 4 is derived to quantify the (dis)advantage of a new technology in terms of overall environmental impacts. For example, considering the global morphine market of 1.16 kt/year [98,99],

Figure 4



Collaborative workflow scheme to guide pharmaceutical industry toward sustainability.

substituting the extraction-based production (2741 $kgCO_2eq/kg$) [66] with synthetic production (1506 $kgCO_2eq/kg$) [10••] would potentially reduce the global CC impact for this product by around 1.43 $MtCO_2eq/year$. Environmentally assessing biological morphine production [100] could quantitatively showcase its difference from the chemical production alternatives. Though such an environmental impact comparison of chemical and biological production of a pharmaceutical is not found in literature, the potential is illustrated by biological polymer production that is reported to reduce the environmental impacts by 36–140% among different polymers [24], which would translate into up to 4.45 $MtCO_2eq/year$ reduction for global morphine market as an example case.

$$Impact = Population \times Affluence \times Technology\,(IPAT\ equation) \quad (1)$$

$$Impact = Population \times \frac{Product}{Population} \times \frac{Impact}{Product} \quad (2)$$

$$Impact = Market\quad volume \times \frac{Impact}{Product} \quad (3)$$

$$\Delta Impact = Market\quad volume \times \left[\left(\frac{Impact}{Product}\right)_{old} - \left(\frac{Impact}{Product}\right)_{new}\right] \quad (4)$$

Accordingly, an interdisciplinary workflow was designed between biotechnology and sustainability experts (Figure 4). As visualized, the initial step would be a market study by sustainability experts to list the products based on their market volume. The next objective of sustainability experts is assessing the pharmaceuticals with the highest market volume. In parallel, biotechnology experts would estimate the resources (labor, time, financial) for biorefactoring of high-volume pharmaceuticals. The subsequent stage is the determination of the target compounds to biorefactor via active discussion of experts (e.g.

meetings, panels) based on their respective lists of highest priority and feasibility. For compounds found infeasible to biorefactor, alternative techniques could be sought to mitigate their environmental impacts. After determining target compounds, novel bio-based technologies contributing to the highest positive sustainability impact, that is, ensuring a minimal impact as conceptualized with the $\left(\frac{Impact}{Product}\right)_{new}$ term in Equation 4, should be collaboratively developed. As recently demonstrated [101••], process modeling and analysis by sustainability experts, based on the data provided by biotechnology experts, is key to optimizing new technologies during early-stage process development. For instance, if nutrient media for the microbial factory constitute a significant portion of the environmental impacts, research efforts could focus on modifying the strain to grow on more sustainable feed alternatives. If the usage of certain solvents in downstream purification is adding significantly to the overall impacts, solvents with lower environmental impacts and/or requiring lower quantities (also considering the energy for recycling in such cases) could be investigated [101••]. For energy-intensive processes, production locations with cleaner energy grids could be considered [101••]. If initial assessments indicate poor performance on water consumption, eventual facilities with *in situ* water treatment and corresponding process modifications (e.g. ensuring compatible streams for biological treatment units considering toxicity) can be investigated [101••]. If clean-in-place/steam-in-place operations comprise a considerable fraction of the overall impact, continuous processing [101••] or single-use biomanufacturing technologies [102] could improve the process.

Conclusions

The significantly increasing pharmaceuticals consumption necessitates ensuring the sustainability of this impact-intensive industry. Analyzing the existing sustainability assessments of pharmaceutical products revealed that only a minor fraction of them is explored, and the drastic differences in environmental impacts necessitate individual assessments. The inclusion of all impact categories will be crucial in understanding the current sustainability status of the industry, as well as in holistically comparing the benignity of different technologies. Biologically refactoring (semi)synthetic production routes promises to optimize the industry in terms of several economic, environmental, and social sustainability aspects. To efficiently lead the sustainability transition of the industry, bio-refactoring efforts can be targeted to pharmaceuticals with high market volume, relative feasibility for bio-refactoring, and high current environmental impact. Evaluating and enhancing the sustainability performance of novel technologies in the early developmental stages is key to ensuring their highest contribution to the overall sustainability of the pharmaceutical industry.

CRediT authorship contribution statement

Deniz Etit: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. **Samir Meramo:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Ólafur Ögmundarson:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Michael Krogh Jensen:** Conceptualization, Funding acquisition, Project administration, Writing – review & editing. **Sumesh Sukumara:** Conceptualization, Methodology, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Data Availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare no conflict of interest.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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